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Syntheses of 6-Amino-1,2-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol Derivatives

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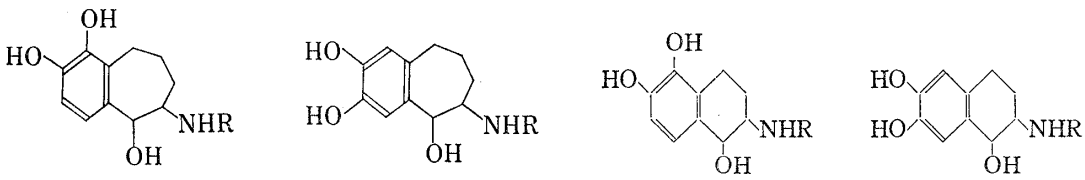
Investigations on the essential conformation of adrenergic catecholamines led us to synthesize 6-amino-1,2-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol derivatives (**1**), which are seven-membered rigid analogues of catecholamines. Although catalytic reduction of the amino ketones (**9** and **10**) leading to the analogues of noradrenaline and isoproterenol (**1a** and **1c**) yielded mixtures of 5,6-*cis* and *trans* isomers, it was found that lithium aluminum hydride reduction of α-hydroxyimino ketone (**12**) gave exclusively *cis*-amino alcohol (**13a**-*cis*) and that reduction of α-acetamido ketone (**14**) with sodium borohydride followed by hydrolysis afforded **13a**-*trans*. Several pairs of 5,6-*cis* and *trans* isomers of **1** were prepared by catalytic reduction of **13a**-*cis* and **13a**-*trans* or their N-substituted derivatives. N-*tert*-Butyl derivative (**1d**-*trans*) was prepared *via* **13d**-*trans* which was obtained by hydrolysis of an azirizino compound (**24**).

Keywords——catecholamine derivative; benzocycloheptene; tetrahydrobenzocycloheptenol; conformationally rigid catecholamine; β-adrenoceptor activity; stereoselective reduction

Pharmacologically active substances having a limited number of permissible conformation provide useful information for the receptor analysis. In the preceding papers we reported the synthesis of 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol derivatives (**3**)[2,3] which are six-membered congeners of adrenergic catecholamines. The potent β-adrenergic stimulating activities exhibited by many of the derivatives **3**[3,4] suggest that functional groups in these molecules occupy the favorable positions to be in contact with the adrenoceptors. The location of the 5,6-di-hydroxyl groups seems to be particularly critical in view of the fact that the 6,7-dihydroxy derivatives (**4**) showed significantly weak activities.[5] In an attempt to investigate the spatial requirement of the aminoethanol moiety in more detail, the study has been extended to the synthesis of 6-amino-1,2-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol derivatives (**1**), in which the saturated six-membered ring in **3** is enlarged



1 **2** **3** **4**

Chart 1

1) Location: *Juso-Honmachi, Yodogawa-ku, Osaka 532, Japan.*
2) Y. Oka, M. Motohashi, H. Sugihara, O. Miyashita, K. Itoh, M. Nishikawa, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **25**, 632 (1977).
3) K. Itoh, M. Motohashi, H. Kuriki, H. Sugihara, N. Inatomi, M. Nishikawa, and Y. Oka, *Chem. Pharm. Bull.* (Tokyo), **25**, 2917 (1977).
4) M. Nishikawa, M. Kanno, H. Kuriki, H. Sugihara, M. Motohashi, K. Itoh, O. Miyashita, Y. Oka, and Y. Sanno, *Life Sci.*, **16**, 305 (1975).
5) M. Kanno, private communication.

to a seven-membered ring. The present paper is concerned with the synthesis of derivatives **1**. It should be mentioned in this connection that the 2,3-dihydroxy analogs (**2**) have recently been synthesized by Khanna *et al.* and reported to possess a weak α-sympathomimetic activity.[6]

The first synthetic approach to **1** is outlined in Chart 2. 1,2-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**5**), which was prepared by a modification of the known procedure,[7] was converted to α-hydroxyimino ketone (**6**) by treatment with isoamyl nitrite in ether in the presence of hydrogen chloride. Catalytic hydrogenation of **6** over palladium-carbon afforded 6-amino-1,2-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**7**), which was allowed to react with acetone and lithium cyanoborohydride[8] to give the 6-isopropylamino derivative (**8**). Treatment of **7** and **8** with 47% hydrobromic acid effected demethylation to give 1,2-dihydroxy derivatives, **9** and **10**, respectively. Compounds **9** and **10** were respectively led to 6-amino and 6-isopropylamino derivatives of **1** (**1a** and **1c**), conformationally rigid derivatives of adrenaline and isoproterenol, by catalytic hydrogenation over platinum oxide in water. These products, however, proved to be a mixture of 5,6-*cis* and *trans* isomers from the observation of the nuclear magnetic resonance (NMR) spectra, which are to be discussed later. The result that indicated the catalytic reduction of the 5-carbonyl group proceeded without stereoselectivity.[2,3]

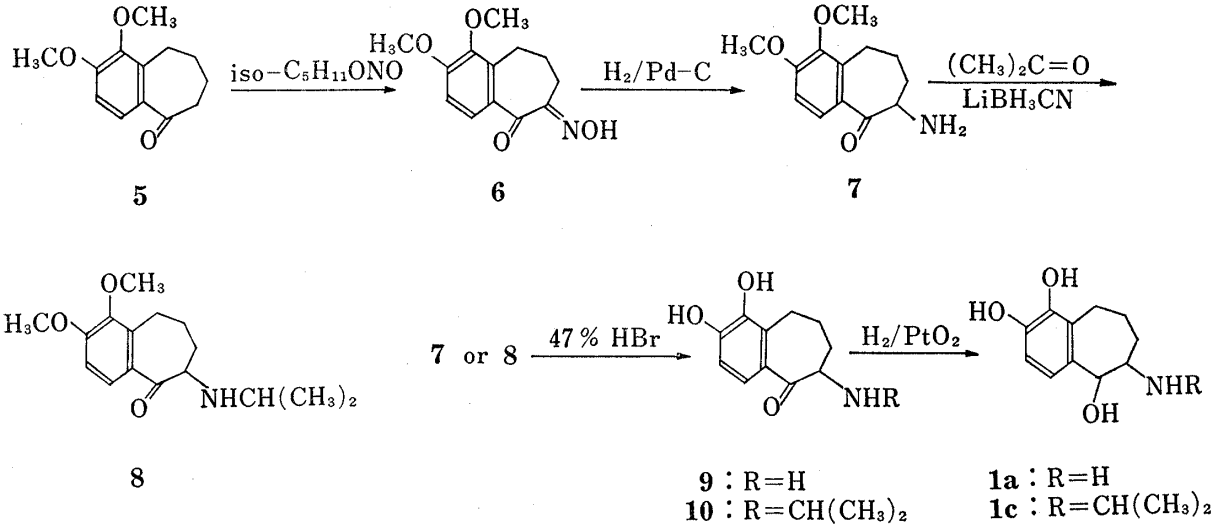


Chart 2

In an effort to obtain the *cis* and *trans* derivatives, investigations were undertaken to effect stereospecific reduction of the 5-carbonyl group. Since both 5,6-dihydroxyamino ketone (**9** and **10**) and **1** were found to be very unstable under alkaline conditions, no reducing method other than catalytic hydrogenation could be applied to the reduction of **9** or **10**. On the other hand, when the carbonyl group was reduced at the stage of **7** or **8**, the resulting amino alcohol moiety could not survive the subsequent demethylation under a drastic condition. Therefore, homologous compounds bearing 1,2-dibenzyloxy group, which would be readily unmasked by mild catalytic hydrogenation at the final step of the synthesis, were employed as the materials. Thus, 1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**11**), prepared by demethylation of **5** with aluminum chloride and the subsequent benzylation,

6) *a*) B. Lal, J.M. Khanna, and N. Anand, *J. Med. Chem.*, **15**, 23 (1972); *b*) G.B. Singh, R.C. Srimal, and B.N. Dhawan, *Japan. J. Pharmacol.*, **24**, 5 (1974); *c*) J.M. Khanna, B. Lal, V.K. Tandon, and N. Anand, *J. Indian Chem. Soc.*, **51**, 289 (1974).
7) P.G. Gardner, W.J. Horton, G. Thompson, and R.R. Twelves, *J. Am. Chem. Soc.*, **74**, 5527 (1952).
8) R.F. Borch, M.D. Bernstein, and H.D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

was led to hydroxyimino ketone (**12**). Reduction of **12** with lithium aluminum hydride afforded 6-amino-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol. The NMR spectrum of the compound in $CDCl_3$ showed a singlet ($J_{5,6}=0$) due to C_5–H at δ 4.72. According to Khanna's study on 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol,[6] one isomer having a coupling constant ($J_{5,6}$) of 1 Hz has been assigned the *cis* and the other with $J_{5,6}=8$ Hz the *trans*. Hence the obtained compound was assigned the *cis* isomer (**13a**-*cis*).[9]

On the other hand, **12** was catalytically reduced over Raney nickel in acetic acid-acetic anhydride to give 6-acetamido-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**14**). Treatment of **14** with sodium borohydride effected stereoselective reduction to *trans*-6-acetamido-5-hydroxy derivative (**15**-*trans*). Alkaline hydrolysis of **15**-*trans* afforded **13a**-*trans*, the NMR spectrum of which showed a doublet with $J_{5,6}=10$ Hz at δ 4.73. Compound **13a**-*trans*, was also derived from its *cis* isomer (**13a**-*cis*) by the following route: Compound **13a**-*cis* was treated with acetic anhydride in methanol[6c] to give *cis*-acetamido alcohol (**15**-*cis*), which was converted to the *trans* isomer (**13a**-*trans*) by Jones oxidation followed by sodium borohydride reduction. The conversion of **13a**-*cis* to **13a**-*trans* was also attained by a similar route employing a series of N-ethoxycarbonyl compounds, *i.e.* Schotten-Bauman reaction of **13a**-*cis* with ethyl chlorocarbonate to give *cis*-N-ethoxycarbonyl derivative (**16**-*cis*), Jones oxidation of **16**-*cis* leading to a ketone (**17**), reduction of **17** with sodium borohydride to give the *trans*-ethoxycarbonyl derivative (**16**-*trans*), and alkaline hydrolysis of **16**-*trans*.

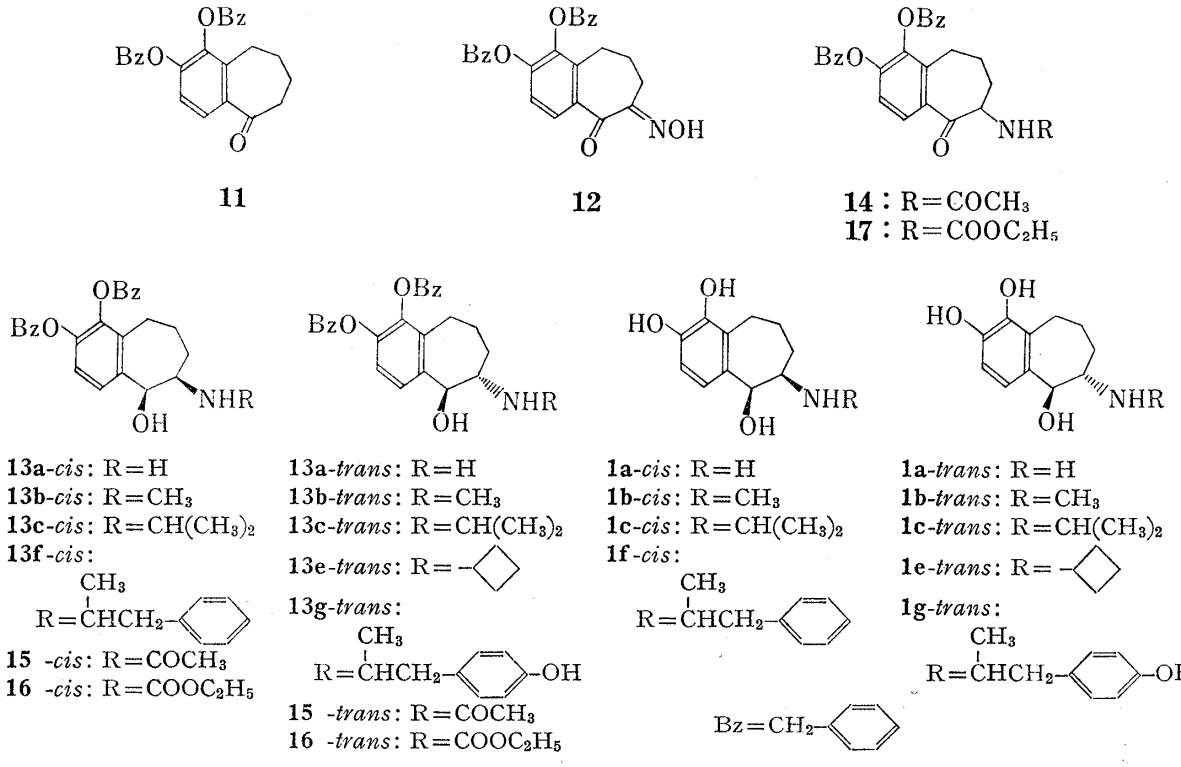


Chart 3

Compounds **13a**-*cis* and **13a**-*trans* were respectively led to **1a**-*cis* and **1a**-*trans*, the *cis* and *trans* derivatives of noradrenaline, by catalytic hydrogenation over palladium-charcoal. The reductive alkylation of **13a**-*cis* and **13a**-*trans* with a variety of ketones in the presence

9) In this paper configurations of the substituents at C_5–C_6 in the benzocycloheptene derivatives are represented by affixing "*cis*" or "*trans*" behind the compound number. A compound number without the affix denotes that the compound consists of a mixture of 5,6-*cis* and *trans* isomers or that the both isomers are discussed together.

of lithium cyanoborohydride afforded N-substituted derivatives of each isomer (**13c**-*cis*, **13f**-*cis*,[10] **13c**-*trans*, **13e**-*trans* and **13g**-*trans*[10]), which were catalytically hydrogenated to give **1** derivatives (**1c**-*cis*, **1f**-*cis*, **1c**-*trans*, **1e**-*trans* and **1g**-*trans*). However, the preparation of N-methyl derivatives (**13b**-*cis* and **13b**-*trans*) by a similar reductive alkylation of **13a**-*cis* and **13a**-*trans* with formaldehyde proved to be difficult owing to the formation of the N,N-dimethyl derivative. Therefore, the synthesis of the rigid adrenaline derivatives, **1b**-*cis* and **1b**-*trans*, were achieved by lithium aluminum hydride reduction of the N-ethoxycarbonyl derivatives (**16**-*cis* and **16**-*trans*) to give N-methyl derivatives (**13b**-*cis* and **13b**-*trans*), followed by debenzylation by the catalytic hydrogenation.

It has been shown that N-substitution of a catecholamine derivative with a *tert*-butyl group has often provided a potent β-adrenergic stimulant.[11] In the present benzocycloheptene series it was considered to be also of interest to synthesize the 6-*tert*-butylamino derivative (**1d**). Our initial approach to prepare the N-*tert*-butyl derivative by substitution of α-bromo ketone (**18**), which was obtained by bromination of **5**, with *tert*-butylamine was unsuccessful, affording a dehydrogenated tropon derivative (**19**). A successful synthesis was ultimately achieved employing the procedure involving an azirizine intermediate[12,13] as shown in Chart 4. Thus, benzocycloheptenone (**11**) was converted to the bromohydrin derivative (**22**) by a sequence of reactions; reduction to alcohol (**20**), dehydration to **21** and treatment with N-bromosuccimide. Compound (**22**) was heated with *tert*-butylamine to undergo rearranged substitution affording the 5-*tert*-butylamino-6-hydroxy derivative (**23**),

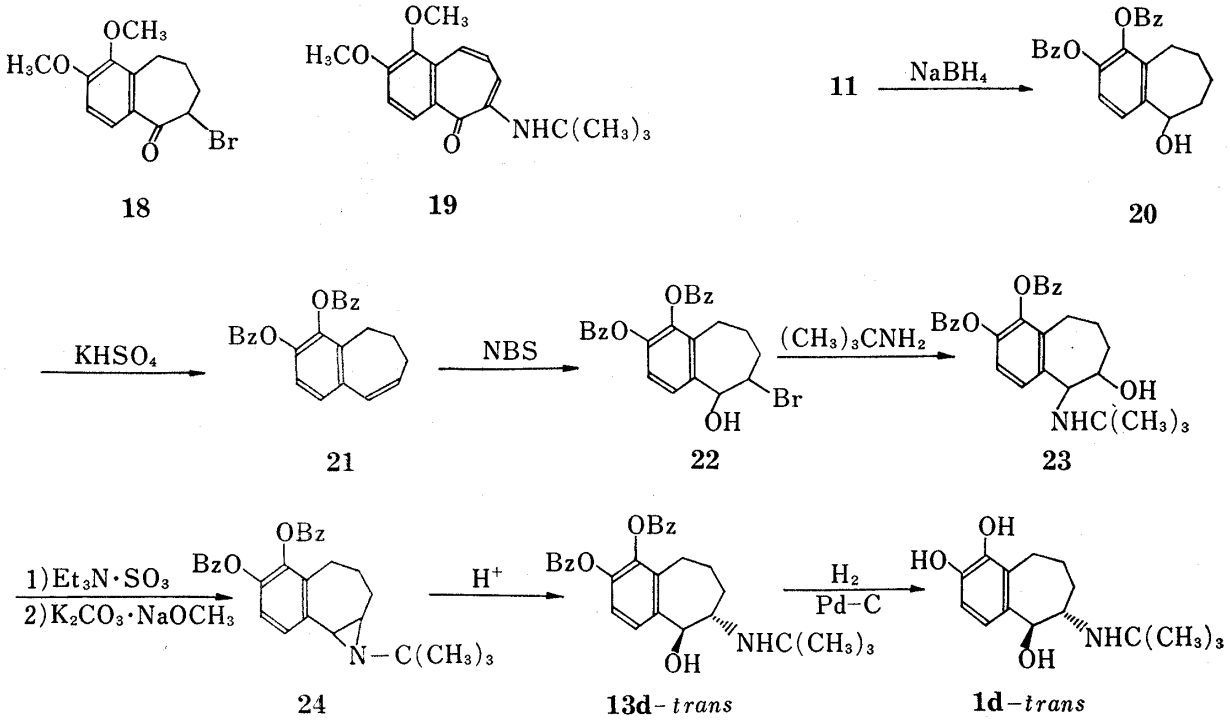


Chart 4

10) We have no evidence at present concerning the stereochemistry of the substituent at the α-carbon in R, although asymmetric induction might have arisen owing to the two asymmetric centers at the 5 and 6-positions in **13a**.

11) See for example, D.J. Triggle, "Medicinal Chemistry," 3rd ed., Vol. 2, ed. by A. Burgerd, Willey-Interscience, Inc., New York, N.Y., 1970, p. 1235.

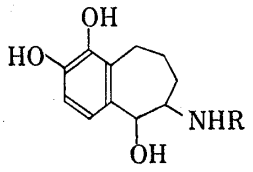
12) H. Sugihara, K. Ukawa, A. Miyake, K. Itoh, and Y. Sanno, *Chem. Pharm. Bull.* (Tokyo), **26**, 394 (1978).

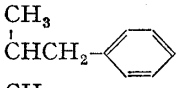
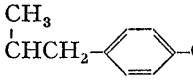
13) H. Sugihara, K. Ukawa, A. Miyake, and Y. Sanno, *Chem. Pharm. Bull.* (Tokyo), **26**, 411 (1978).

the structure of which was inferred from analogy to the case of previously reported tetralin derivatives[12] and from the inconsistency of the compound with the derivative (**13d**). Treatment of **23** with the triethylamine-sulfur trioxide complex followed by work-up with potassium carbonate and sodium methoxide gave an azirizine derivative (**24**). Acid hydrolysis of **24** in dilute sulfuric acid-dioxane yielded predominantly *trans*-1,2-dibenzyloxy-6-*tert*-butylamino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (**13d**-*trans*), $J_{5,6}$=8 Hz, in contrast to the result in the tetralin series[12] where the *cis* isomer was afforded as the major product under the same conditions. Debenzylation of **13d**-*trans* by catalytic hydrogenation yielded **1d**-*trans*.

Compounds **1** synthesized by the above methods are summarized in Table I.

TABLE I. 6-Substituted Amino-1,2-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol(**1**)



No.	R	Salt	Yield[a] (%)	mp (°C) (dec.)	NMR δ[b] (J Hz)[c]	Formula	Analysis (%) Calcd. (Found) C	H	N
1a	H	HBr	20	Indefinite[d]		$C_{11}H_{15}NO_3\cdot HBr$	— (—)	— (—)	— (—)
1a-*cis*	H	Fumarate	50	197—200	4.70(0)	$C_{11}H_{15}NO_3\cdot 1/2C_4H_4O_4\cdot 1/2H_2O$	56.51 (56.86)	6.20 (6.43)	5.07 (4.81)
1a-*trans*	H	Fumarate	38	183—185	4.68(9)	$C_{11}H_{15}NO_3\cdot C_4H_4O_4\cdot 1/2H_2O$	53.89 (53.87)	6.03 (6.43)	4.19 (4.61)
1b-cis	CH_3	Fumarate	74	176—178	4.85(0)	$C_{12}H_{17}NO_3\cdot 1/2C_4H_4O_4\cdot H_2O$	56.17 (55.58)	7.07 (6.58)	4.68 (4.50)
1b-*trans*	CH_3	Fumarate	72	210—212	4.77(8)	$C_{12}H_{17}NO_3\cdot 1/2C_4H_4O_4$	59.77 (59.39)	6.81 (6.66)	4.98 (5.04)
1c	$CH(CH_3)_2$	HBr	70	145—150	—	$C_{14}H_{21}NO_3\cdot HBr$	50.61 (50.28)	6.67 (6.97)	4.22 (4.23)
1c-*cis*	$CH(CH_3)_2$	Fumarate	81	186—189	4.80(0)	$C_{14}H_{21}NO_3\cdot 1/2C_4H_4O_4\cdot 1/2H_2O$	60.36 (60.76)	7.28 (7.37)	4.40 (4.34)
1c-*trans*	$CH(CH_3)_2$	Fumarate	64	184—186	4.78(8)	$C_{14}H_{21}NO_3\cdot 1/2C_4H_4O_4\cdot H_2O$	58.70 (58.48)	7.70 (7.81)	4.28 (4.47)
1d-*trans*	$C(CH_3)_3$	Fumarate	72	215—216	4.38(7)	$C_{15}H_{23}NO_3\cdot 1/2C_4H_4O_4\cdot 1/2H_2O$	61.42 (61.16)	7.88 (7.78)	4.21 (3.84)
1e-*trans*		Fumarate	68	169—171	4.70(8)	$C_{15}H_{21}NO_3\cdot 1/2C_4H_4O_4\cdot 1/2H_2O$	61.80 (62.27)	7.32 (7.33)	4.24 (4.29)
1f-*cis*		Fumarate	40	137	4.88(0)	$C_{20}H_{25}NO_3\cdot C_4H_4O_4$	62.45 (62.52)	6.77 (6.59)	3.04 (3.16)
1g-*trans*		Fumarate	57	140—145	4.86(10)	$C_{20}H_{25}NO_4\cdot 1/2C_4H_4O_4\cdot 2H_2O$	60.40 (60.81)	7.14 (7.31)	3.20 (3.14)

a) Yield of the final process.
b) Chemical shift of C_5–H. (100MHz in d_6-DMSO–D_2O).
c) Coupling constant between C_5–H and C_6–H.
d) Amorphous.

The β_1- and β_2-adrenoceptor activities of derivatives **1** were measured *in vitro* using, respectively, isolated aterial preparations and tracheal strips of guinea pig according to the methods described in the preceding paper.[4] It was found that derivatives **1** showed rather weaker activities than the corresponding six-membered derivatives **3** for both the aterial and tracheal preparations. However, **1** generally showed superior β_2-adrenoceptor selectivity compared with the corresponding **3**.

Experimental[14]

1,2-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (5)——To a stirred solution of *tert*-BuOK prepared *in situ* from K (25 g) and *tert*-BuOH (500 ml) was added dropwise a solution of 2,3-dimethoxybenzaldehyde (45 g) and methyl crotonate (47 g) in *tert*-BuOH (100 ml). After stirring overnight, the mixture was poured into water (2 l) and extracted with AcOEt (300 ml). The aqueous solution was acidified with HCl and extracted with $CHCl_3$ (1 l). The extract was dried over Na_2SO_4 and evaporated to give crude 5-(2,3-dimethoxyphenyl)penta-2,4-dienoic acid (60 g) as an oil, which was solidified by the addition of petroleum ether. The obtained acid was dried over P_2O_5 *in vacuo*, dissolved in EtOH (500 ml), and hydrogenated over 5% palladium-carbon (10 g) at room temperature under atmospheric pressure. When the absorption of hydrogen ceased, the catalyst was filtered off, and the filtrate was evaporated *in vacuo* to give 5-(2,3-dimethoxyphenyl)pentanoic acid[7] (60 g) as an oil. A mixture of the obtained pentanoic acid (58 g), dry benzene (200 ml) and PCl_5 (52 g) was refluxed for 30 min and then cooled to 5°. To the obtained solution was added dropwise a solution of anhydrous $SnCl_4$ (35 ml) in dry benzene (100 ml) under stirring. After stirring for 6 hr at room temperature, the mixture was poured into ice-10% HCl (excess), and extracted with AcOEt (1 l). Evaporation of the extract and recrystallization of the residue from petroleum ether–*n*-hexane afforded **5** (35 g, 59%) as colorless crystals, mp 49—50° (lit.[7] 49—50.5°).

1,2-Dimethoxy-6-hydroxyimino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (6)——To a stirred solution of **5** (12.6 g) in 4% HCl–ether (125 ml) was added dropwise a solution of iso-amyl nitrite (25 g) in ether (125 ml). After being stirred for 20 min, precipitated colorless crystals were collected by filtration to give **6** (8.3 g, 58%). The filtrate was evaporated to dryness and the residue was purified by silica gel column chromatography (acetone, benzene=1:2) to afford additional **6** (0.8 g, 5.6%), mp 165—166.5°. *Anal.* Calcd. for $C_{13}H_{15}NO_4$: C, 62.46; H, 6.07; N, 5.62. Found: C, 62.18; H, 6.13; N, 5.70. IR ν_{max}^{Nujol} (cm^{-1}): 3200 (OH), 1690 (C=O).

6-Amino-1,2-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (7)——A solution of **6** (2 g) in MeOH (20 ml) containing 20% HCl–EtOH (4 ml) was hydrogenated over 5% palladium-carbon (0.5 g) at room temperature under atmospheric pressure until the absorption of hydrogen ceased. The mixture was filtered and the filtrate was evaporated *in vacuo*. Recrystallization of the residue from AcOEt gave **7**·HCl (2.1 g, 96%) as colorless crystals, mp 158—163°. *Anal.* Calcd. for $C_{13}H_{17}NO_3$·HCl: C, 57.46; H, 6.68; N, 5.16. Found: C, 56.91; H, 6.68; N, 4.81. IR ν_{max}^{Nujol} (cm^{-1}): 1680 (C=O).

1,2-Dimethoxy-6-isopropylamino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (8)——A mixture of **7**·HCl (1.5 g), acetone (120 ml), $LiBH_3CN$ (1.8 g) and MeOH (30 ml) was stirred at room temperature for 2 hr. Under ice-cooling the mixture was acidified with 10% HCl, neutralized with $NaHCO_3$ and extracted with ether (100 ml). After drying over Na_2SO_4, to the solution was added dropwise 20% HCl–EtOH (10 ml). The resulting colorless crystals were collected by filtration to give **8**·HCl (1.4 g, 86%), mp 172—174°. *Anal.* Calcd. for $C_{16}H_{23}NO_3$·HCl: C, 61.23; H, 7.33; N, 4.46. Found: C, 61.25; H, 7.54; N, 4.16. IR ν_{max}^{Nujol} (cm^{-1}): 1690 (C=O).

6-Amino-1,2-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (9)——A mixture of **7**·HCl (2 g) and 47% HBr (30 ml) was refluxed with stirring at 160—170° for 3 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in MeOH (100 ml), decolorized with activated carbon, and evaporated *in vacuo*. Trituration of the residue with acetone–ether gave **9**·HBr (1.7 g, 80%) as colorless powder, mp 143—145°. *Anal.* Calcd. for $C_{11}H_{13}NO_3$·HBr: C, 45.85; H, 4.51; N, 4.86. Found: C, 45.58; H, 4.78; N, 4.39.

1,2-Dihydroxy-6-isopropylamino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (10)——Demethylation of **8** (1.4 g) with 47% HBr was carried out in a similar manner to that in the preparation of **9**. Recrystallization of the product from acetone–ether afforded **10**·HBr (1.0 g, 68%) as colorless powder, mp 227—232°. *Anal.* Calcd. for $C_{14}H_{19}NO_3$·HBr: C, 50.92; H, 6.10; N, 4.24. Found: C, 50.64; H, 6.30; N, 4.33. IR ν_{max}^{Nujol} (cm^{-1}): 3400, 3250 (OH), 1680 (C=O).

1,2-Dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (11)——A mixture of **5** (50 g), $AlCl_3$ (100 g) and benzene (500 ml) was refluxed for 1 hr with stirring. After cooling the reaction mixture was poured into excess 10% HCl and extracted with AcOEt (1 l). The extract was dried over Na_2SO_4 and condensed *in vacuo* to give 1,2-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (35 g, 80%) as colorless prisms, mp 178—182°. *Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.54; H, 6.25. This compound (35 g) was dissolved in EtOH (300 ml) containing benzyl chloride (51 g), K_2CO_3 (28 g), KI (3.3 g) and small amount of $Na_2S_2O_3 \cdot 5H_2O$. The resulting mixture was heated under reflux with stirring for 1 hr. After addition of a solution of KOH (11 g) in EtOH (50 ml), reflux was continued for further 1 hr. The mixture was poured into excess water and extracted with $CHCl_3$ (700 ml). The extract was dried over Na_2SO_4

14) All melting points were determined on a micro hot-stage apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Hitachi 215 spectrophotometer. NMR spectra were recorded on Varian T-60 or HA-100 using Me_4Si as a standard. The mass spectra (MS) were determined on a Hitachi RMU-6D mass spectrometer.

and evaporated *in vacuo* to give **11** (68 g, 100%) as a brown oil. IR ν_{max}^{Nujol} (cm^{-1}): 1670 (C=O). NMR ($CDCl_3$) δ: 1.6—2.0, 2.6—3.2 (4H), 5.0 (2H), 5.2 (2H), 6.8—7.6 (12H).

1,2-Dibenzyloxy-6-hydroxyimino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (12)——To an ice-cooled solution of **11** (16.2 g) in 4% HCl–ether (80 ml) was added dropwise a solution of isoamyl nitrite (18 g) in ether (40 ml) with stirring. After stirring for 30 min the resulting solid was collected by filtration to give **12** (12 g, 69%) as colorless needles. mp 178—179°. *Anal.* Calcd. for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.78; N, 3.49. Found: C, 74.77; H, 5.79; N, 3.47. IR ν_{max}^{Nujol} (cm^{-1}): 3200 (OH), 1690 (C=O). NMR ($CDCl_3+D_2O$) δ: 1.6—2.2 (2H, m), 2.4—3.2 (4H, m), 5.0 (2H, s), 5.2 (2H, s), 6.9—7.8 (12H, m).

***cis*-6-Amino-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (13a-*cis*) (Table II)**——To a solution of **12** (4 g) in tetrahydrofuran (THF) (100 ml) was added $LiAlH_4$ (5 g) and the mixture was refluxed for 1 hr with stirring. Under ice-cooling water was added dropwise to decompose excess $LiAlH_4$. To the mixture was added AcOEt (300 ml) and the precipitate was filtered off. The filtrate was dried over Na_2SO_4 and evaporated *in vacuo* to give crude **13a**-*cis* (2.7 g) as colorless powder, recrystallization of which from MeOH afforded 2 g (51%) of colorless prisms.

6-Acetamido-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (14)——i) A solution of **12** (1 g) in AcOH (20 ml) and Ac_2O (4 ml) was hydrogenated over Raney nickel (wet, 1 g) at room temperature under atmospheric pressure until 2 equivalent hydrogen was absorbed. After the catalyst was removed by filtration, the filtrate was diluted with excess water and extracted with $CHCl_3$ (50 ml). The extract was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated *in vacuo*. Recrystallization of the residue from ether–petroleum ether afforded **14** (0.35 g, 36%) as colorless prisms. mp 133—136°. *Anal.* Calcd. for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; H, 3.26. Found: C, 75.48; H, 6.23; N, 2.99.

ii) To a stirred solution of **13a-*cis*** (4.7 g) in MeOH (200 ml) was added dropwise Ac_2O (5 g). After standing for 15 min, the reaction mixture was condensed to a half volume under room temperature and diluted with water (100 ml). Filtration of the resulting precipitate afforded **15**-*cis* (4.9 g, Table II), which was dissolved in acetone (100 ml). To the solution was added dropwise CrO_3–H_2SO_4 (Jones reagent) with stirring at room temperature until the orange color of the reagent remained. After the excess reagent was consumed by addition of MeOH, insoluble substance was filtered. The filtrate was poured into excess water and extracted with $CHCl_3$ (100 ml). The extract was washed with 10% $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residual oil was chromatographed on silica gel, using acetone–benzene (1: 4) as the eluant, to give **14** (2 g, 42%).

***trans*-6-Acetamido-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (15-*trans*) (Table II)**——To a stirred solution of **14** (2 g) in MeOH (100 ml) was added portionwise $NaBH_4$ (2 g) at room temperature. The reaction mixture was diluted with water (500 ml) and the resulting solid was collected by filtration. Recrystallization from $CHCl_3$ afforded **15**-*trans* (1 g) as colorless prisms. IR ν_{max}^{Nujol} (cm^{-1}): 1630 (C=O). NMR ($CDCl_3+d_6$-DMSO) δ: 1.8 (3H, s), 4.6 (1H, d, J=8 Hz), 4.9 (2H, s), 5.2 (2H, s).

***cis*-1,2-Dibenzyloxy-6-ethoxycarbonylamino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (16-*cis*) (Table II)**——To a mixture of **13a**-*cis* (1.17 g), AcOEt (50 ml), cracked ice (50 g), water (50 g) and K_2CO_3 was added dropwise a solution of ethyl chlorocarbonate (0.33 g) in AcOEt (25 ml) within a period of 10 min, while the mixture was vigorously stirred. After addition of cracked ice (50 g), stirring was continued for further 15 min. The organic layer was separated, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was triturated with ether (20 ml) and filtered to give colorless powder. Upon evaporation of the filtrate **16**-*cis* (0.35 g) was obtained as colorless crystals. On the other hand the above colorless powder, which consisted mainly of **16**-*cis* and small amount of the *trans* isomer isomerized during the reaction, was dissolved in $CHCl_3$ (10 ml). Evaporation of the solution *in vacuo*, followed by treatment of the residue with ether (10 ml) in the same manner as above gave additional **16**-*cis* (0.2 g). IR ν_{max}^{Nujol} (cm^{-1}): 1670 (C=O). NMR ($CDCl_3+D_2O$) δ: 1.2 (3H, t, J=7 Hz), 4.2 (2H, q, J=7 Hz), 4.6 (1H, s), 5.0 (2H, s), 5.2 (2H, s).

1,2-Dibenzyloxy-6-ethoxycarbonylamino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (17)——**16**-*cis* (6 g) was oxidized with Jones reagent in a similar manner to that in the preparation of **14**. The product was crystallized from ether to give **17** (3.8 g, 64%) as colorless powder. mp 120—122°. *Anal.* Calcd. for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 73.38; H, 6.61; N, 2.99. IR ν_{max}^{Nujol} (cm^{-1}): 1680, 1660 (C=O). NMR ($CDCl_3$) δ: 1.3 (3H, t, J=7 Hz), 4.2 (2H, q, J=7 Hz), 5.0 (2H, s), 5.3 (2H, s).

***trans*-1,2-Dibenzyloxy-6-ethoxycalbonylamino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (16-*trans*) (Table II)**——A solution of **17** (2.5 g) in a mixture of MeOH (30 ml) and $CHCl_3$ (10 ml) was allowed to react with $NaBH_4$ (2.5 g) as described for the preparation of **15**-*trans*. Recrystallization of the product from MeOH afforded **16**-*trans* (1.8 g) as colorless powder. IR ν_{max}^{Nujol} (cm^{-1}): 1680 (C=O). NMR ($CDCl_3+D_2O$) δ: 1.2 (3H, t, J=7 Hz), 4.1 (2H, q, J=7 Hz), 4.6 (1H, d, J=7 Hz), 4.9 (2H, s), 5.1 (2H, s).

***trans*-6-Amino-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (13a-*trans*) (Table II)**——A solution of **15**-*trans* or **16**-*trans* (1 g) in 10% aqueous EtOH containing NaOH (10 g) was heated under reflux for 8 hr. The reaction mixture was diluted with water (20 ml), cooled and the resulting precipitate was collected by filtration to give **13a**-*trans* (0.8 g) as colorless prisms. The TsOH salt of **13a**-*trans* was obtained as colorless prisms by addition of MeOH solution of TsOH to the free base of **13a**-*trans* followed by dilution with ether. NMR ($CDCl_3$) δ: 4.3 (1H, d, J=7 Hz), 4.8 (2H, s), 5.1 (2H, s).

***cis* or *trans*-1,2-Dibenzyloxy-6-methylamino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (13b-*cis* or 13b-*trans*) (Table II)**——The reduction of *cis* or *trans*-6-ethoxycarbonyl compound (**16**-*cis* or **16**-*trans*) with $LiAlH_4$ was carried out by the similar procedure to that described for the preparation of **13a**-*cis*. The obtained crude *cis* or *trans* product was recrystallized from ether to give pure **13b**-*cis* or **13b**-*trans* respectively as colorless powder.

***cis*-6-Substituted Amino-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (13c-*cis* and 13f-*cis*) (Table II)**——To a stirred solution of **13a**-*cis* (1 g) in a mixture of MeOH (50 ml) and acetone (10 g) was added $LiBH_3CN$ (2 g) and one drop of 20% HCl–EtOH. After standing overnight, the reaction mixture was acidified with 10% HCl under cooling, diluted with excess water, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$ (50 ml). The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was crystallized from ether to give **13c**-*cis* (0.7 g) as colorless powder. In a similar manner **13a**-*cis* was allowed to react with phenylacetone to give **13f**-*cis*.

***trans*-6-Substituted Amino-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (13c-*trans*, 13e-*trans* and 13g-*trans*) (Table II)**——**13a**-*trans*·TsOH was alkylated with a ketone in the presence of $LiBH_3CN$ in a similar manner to that for the preparation of **13c**-*cis* to give *trans*-N-alkylated products (**13c**-*trans*, **13e**-*trans* and **13g**-*trans*). The base of these compounds was obtained as an oil, which was converted fumaric acid salt, colorless crystalline powder.

6-Bromo-1,2-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (18)——To a stirred solution of **5** (3 g) in ether (10 ml) was added Br_2 (2.4 g) and the stirring was continued for further 50 min. The reaction mixture was evaporated, diluted with H_2O, and extracted with AcOEt (100 ml). The extract was dried over Na_2SO_4 and evaporated to give an oil, which was dissolved in MeOH. The resulting solution was decolorized with activated carbon and evaporated to dryness. Recrystallization of the residue from petroleum ether gave **18** (2.6 g, 64%) as colorless prisms, mp 66—68°. *Anal.* Calcd. for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05. Found: C, 52.63; H, 4.59. IR ν_{max}^{Nujol} (cm^{-1}): 1690 (C=O). NMR ($CDCl_3$) δ: 3.8 (3H, s), 3.9 (3H, s), 4.9 (1H, t, $J=6$ Hz).

6-*tert*-Butylamino-1,2-dimethoxy-5*H*-benzocyclohepten-5-one (19)——A mixture of **18** (0.7 g), CH_3CN (20 ml) and *tert*-butylamine (0.35 g) was heated in a sealed tube at 130—140° for 6 hr. After cooling, the solution was evaporated, diluted with water, and extracted with ether (100 ml). After evaporation of ether, the residue was submitted to column chromatography (acetone–benzene=1: 30) to give **19** (0.3 g, 45%) as a yellow oil. IR ν_{max}^{liquid} cm^{-1}: 1580 (C=O), 3330 (NH). MS *m/e*: 287 (M^+). NMR ($CDCl_3$): δ 1.5 (9H, s), 3.9, 4.0 (6H, s), 6.4—8.7 (5H, m).

1,2-Dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (20)——To a stirred solution of **11** (10 g) in MeOH (100 ml) was added portionwise $NaBH_4$ (3.3 g) at room temperature. After being stirred for further 15 min, the mixture was diluted with excess water and extracted with $CHCl_3$ (200 ml). The extract was dried over Na_2SO_4, evaporated *in vacuo* to give **20** as an oil, which was crystallized upon addition of ether–petroleum ether as colorless needles (7.5 g, 75%), mp 112—113°. *Anal.* Calcd. for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 79.86; H, 7.00. IR ν_{max}^{Nujol} (cm^{-1}): 3300 (OH).

3,4-Dibenzyloxy-6,7-dihydro-5*H*-benzocycloheptene (21)——A mixture of **20** (7.5 g), $KHSO_4$ (1.5 g) and benzene (300 ml) was heated under reflux for 1 hr with stirring. The reaction mixture was washed with water, dried over Na_2SO_4 and evaporated. Recrystallization of the residue from ether–petroleum ether gave **21** (7.1 g, 99%) as colorless prisms, mp 157—160°. *Anal.* Calcd. for $C_{25}H_{24}O_2$: C, 84.24; H, 6.79. Found: C, 84.00; H, 6.89. NMR ($CDCl_3$) δ: 1.6—2.2 (2H, m), 2.2—2.6 (2H, m), 2.8—3.2 (2H, m), 5.0 (2H, s), 5.2 (2H, s), 5.6—6.0 (1H, m), 6.4 (1H, d, $J=10$ Hz), 6.7—7.6 (12H, m).

6-Bromo-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (22)——To an ice-cooled mixture of **21** (7.1 g), dimethyl sulfoxide (DMSO) (200 ml) and water (7 ml) was added N-bromosuccinimide (7.2 g) with vigorous stirring under nitrogen. After being stirred for further 10 min, the reaction mixture was diluted with excess water and extracted with benzene (500 ml). The extract was thoroughly washed with water, dried over Na_2SO_4, and evaporated. The residual oil was crystallized from ether–petroleum ether to give **22** (8.15 g, 89%) as colorless crystalline powder, mp 107—109°. *Anal.* Calcd. for $C_{25}H_{25}BrO_3$: C, 66.23; H, 5.56. Found: C, 66.99; H, 5.58. IR ν_{max}^{Nujol} (cm^{-1}): 3300 (OH).

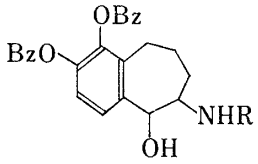
1,2-Dibenzyloxy-5-*tert*-butylamino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ol (23)——A mixture of **22** (8.15 g) and *tert*-butylamine (100 ml) was heated at 110—120° in a sealed tube for 2.5 hr. After excess amine was distilled off, to the residue was added excess water and the mixture was extracted with $CHCl_3$ (200 ml). Removal of $CHCl_3$ *in vacuo* afforded an oil which was chromatographed on a column of silica gel (acetone–benzene=1: 9) to give 5.85 g (73%) of **23** as colorless powder. The analytical sample was recrystallized from petroleum ether, mp 98—100°. *Anal.* Calcd. for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 3.14. Found: C, 78.06; H, 8.13; N, 2.99. IR ν_{max}^{Nujol} (cm^{-1}): 3400, 3350 (OH, NH). NMR ($CDCl_3$) δ: 1.1 (9H, s), 5.0 (2H, s), 5.1 (2H, s).

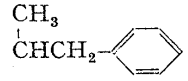
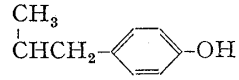
1,2-Dibenzyloxy-5,6-*tert*-butylimino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (24)——A mixture of **23** (5.85 g), $Et_3N{\cdot}SO_3$ (4.8 g) and benzene (200 ml) was heated under reflux for 1 hr. After addition of K_2CO_3 (36 g) the mixture was refluxed with stirring for 30 min. To the mixture was added MeONa (12 g) and the resulting suspension was refluxed with stirring for further 7 hr. The mixture was poured into ice-water and extracted with AcOEt (300 ml). The extract was dried over Na_2SO_4 and evaporated to dryness to give

crude **24** (5.65 g) as an oil. For analysis, a small portion of this product was purified on silica gel by column chromatography (benzene) affording pure **24** as colorless crystalline powder, mp 91—95°. *Anal.* Calcd. for $C_{29}H_{33}NO_2 \cdot H_2O$: C, 78.17; H, 7.92; N, 3.14. Found: C, 78.41; H, 8.11; N, 2.94. MS *m/e*: 427 (M^+). NMR ($CDCl_3$): 1.1 (9H, s), 5.0 (2H, s), 5.1 (2H, s).

1,2-Dibenzyloxy-6-*tert*-butylamino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (13d-*trans*) (Table II)——A solution of **24** (crude 3.65 g) in a mixture of dioxane (200 ml) and 5% H_2SO_4 (180 ml) was allowed to stand for 3 days under room temperature. The reaction mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (200 ml). The extract was dried over Na_2SO_4 and evaporated. The residue was submitted to column chromatography (acetone–benzene = 1 : 4). After evaporation of the eluent, the residue was crystallized from petroleum ether to afford pure colorless crystals (0.8 g), MS *m/e*: 445 (M^+), which were led to the oxalate by the addition of an ethereal solution of oxalic acid.

TABLE II. 6-Substituted Amino-1,2-dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol



No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
13a-*cis*	H	139—141	51	$C_{25}H_{27}NO_3$	77.09 (77.12)	6.99 (6.93)	3.60 (3.62)
13a-*trans*	H	181—183[a] 165—168[b]	78,[c] 88[d]	$C_{25}H_{27}NO_3 \cdot C_7H_8O_3S$[b]	68.43 (68.00)	6.28 (6.15)	2.49 (2.61)
13b-*cis*	CH_3	136—139	57	$C_{26}H_{29}NO_3$	77.39 (77.03)	7.24 (7.08)	3.47 (3.18)
13b-*trans*	CH_3	153—154	46,[e] 34[f]	$C_{26}H_{29}NO_3$	77.39 (77.43)	7.24 (7.19)	3.47 (3.41)
13c-*cis*	$CH(CH_3)_2$	150—152	63	$C_{28}H_{33}NO_3$	77.92 (77.56)	7.71 (7.75)	3.25 (2.95)
13c-*trans*	$CH(CH_3)_2$	207—208	55	$C_{28}H_{33}NO_3 \cdot 1/2C_4H_4O_4$[h]	73.59 (73.30)	7.21 (7.16)	2.86 (2.87)
13d-*trans*	$C(CH_3)_3$	167—169	26	$C_{29}H_{35}NO_3 \cdot C_2H_2O_4$[i]	69.51 (69.24)	6.96 (6.94)	2.62 (2.83)
13e-*trans*		210—212	78	$C_{29}H_{33}NO_3 \cdot 1/2C_4H_4O_4$[h]	74.23 (73.94)	7.03 (6.91)	2.79 (2.76)
13f-*cis*		Indefinite[g]	46	$C_{34}H_{37}NO_3$	80.44 (80.18)	7.35 (7.13)	2.76 (2.95)
13g-*trans*		203—206	77	$C_{34}H_{37}NO_4 \cdot 1/2C_4H_4O_4$[h]	74.33 (73.88)	6.76 (6.86)	2.41 (2.39)
15-*cis*	$COCH_3$	175—179	90	$C_{27}H_{29}NO_4 \cdot H_2O$	72.14 (72.56)	6.95 (6.88)	3.12 (3.11)
15-*trans*	$COCH_3$	219—223	49	$C_{27}H_{29}NO_4 \cdot 1/2H_2O$	73.61 (73.75)	6.86 (6.72)	3.18 (2.91)
16-*cis*	$COOC_2H_5$	113—115	40	$C_{28}H_{31}NO_5$	72.86 (72.89)	6.77 (6.64)	3.04 (3.02)
16-*trans*	$COOC_2H_5$	171—174	72	$C_{28}H_{31}NO_5$	72.86 (72.88)	6.77 (6.68)	3.04 (2.88)

a) Free base. *b*) *p*-Toluenesulfonic acid salt. *c*) Hydrolysis of **16**-*trans*. *d*) Hydrolysis of **15**-*trans*. *e*) $LiAlH_4$ reduction of **16**-*trans*. *f*) $LiAlH_4$ reduction of **17**. *g*) Amorphous. *h*) Fumarate. *i*) Oxalate.

6-Substituted Amino-1,2-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (1) (Table I)——i) A solution of **9**·HBr (0.5 g) in water (5 ml) was hydrogenated over platinum oxide (0.2 g) at room temperature under atmospheric pressure until 1 equivalent hydrogen was consumed. The catalyst was filtered, while the filtrate was added to ether (200 ml). The resulting mixture was allowed to stand overnight and the precipitate was collected by filtration to give **1a**·HBr (0.1 g) as very hygroscopic powder. MS *m/e*: 209 (M^+).

1c·HBr (0.37 g) was prepared from **10**·HBr (0.5 g) by the same method except that the reduction was carried out using 67% aqueous MeOH (15 ml) as the solvent.

ii) Free base of 0.5 g of **13a**-*cis*, **13b**-*cis*, **13c**-*cis*, **13f**-*cis*, **13a**-*trans*, **13b**-*trans*, **13c**-*trans*, **13d**-*trans* or **13g**-*trans* was dissolved in MeOH (20 ml) and hydrogenated over 10% palladium-carbon (0.25 g) under atmospheric pressure at room temperature. The catalyst was removed by filtration and to the filtrate was added equimolar fumaric acid. The mixture was evaporated *in vacuo* at room temperature to afford a viscous syrup, to which was added ether (100 ml) and the mixture was allowed to stand overnight to precipitate colorless powder, which was collected by filtration to afford *cis* or *trans* 1,2-dihydroxy compound, **1a**-*cis*, **1b**-*cis*, **1c**-*cis*, **1f**-*cis*, **1a**-*trans*, **1b**-*trans*, **1c**-*trans*, **1d**-*trans* or **1g**-*trans*, as the fumarate.

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