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Synthesis of 3-Aryl-6-aminocyclohex-2-enol Derivatives

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6-(*N*-Substituted amino)-3-arylcyclohex-2-enol (**7**) was designed as a new type of β-adrenergic blocker on the basis of the X-ray crystallographic data for propranolol. Eight such compounds (**7**) were prepared by a six-step sequence of reactions from 3-arylcyclohex-2-enone (**8**), and tested for β-blocking activity *in vitro*. A weak β-blocking activity was exhibited by 6-(1-methyl-3-phenylpropyl)amino-3-phenylcyclohex-2-enol (**7e**).

Keywords——β-adrenergic blocker; conformationally restricted compound; 3-aryl-6-aminocyclohex-2-enol

An enormous number of β-adrenergic blocking agents have been synthesized and the structure-activity relationships of these compounds have been studied extensively.[1] The structure of β-blocking agents thus far known can be classified into two types, arylethanol derivatives (**1**), exemplified by sotalol, and aryloxypropanolamine derivatives (**2**), exemplified by propranolol, pindolol and most of the currently used β-blockers. Both types involve *N*-substituted aminoethanol as the common structural feature. Therefore, it is assumed that the aryl group in **1** and the aryloxymethyl group in **2** may play an identical role in the interaction with the receptor site. Recently Ammon *et al.*[2] suggested, on the basis of the X-ray crystallographic data for several adrenergic agonists and antagonists, that the OCH_2 bridge in **2** resides in a position corresponding to a part of the aromatic group in **1**. Thus, in the case of propranolol, which was proved to have the conformation shown in **3** and **4**,[3] it was suggested that the C_3–O_4–C_5–C_6 moiety is arranged so as to overlap with the aromatic ring of **1**, and takes the place of the aryl group in the interaction with the receptor. On the other hand, the two benzene rings (rings C and A) of the naphthyl group in pronetalol (**5**), a type-**1** β-blocker, occupy the positions corresponding to the plane of C_3–O_4–C_5–C_6 and ring A, respectively, in **4**.

These speculations, together with our previous findings[4] that β-adrenoceptor activities of adrenergic catecholamines were retained or even enhanced when the aminoethanol moiety was fixed into a tetrahydronaphthalene skeleton as in **6**, led us to design 6-(*N*-substituted amino)-3-arylcyclohex-2-enol (**7**) as a potential β-blocking agent. In the structure **7**, the double bond in the cyclohexene ring corresponds to the C_3–O_4 bond in **4** and a part of the aromatic ring in **5**, and the aminoethanol moiety is incorporated into a six-membered ring with *trans*-configuration, which has been shown to be the most favorable configuration for interaction with the β-adrenoceptor.[4]

Although it remains a subject of controversy whether the conformation of a molecule in the crystalline state is the same as that under physiological conditions, it may be safely said that X-ray crystallographic data represent one of the most energetically stable conformations of the molecule. Quantum chemical calculations have revealed that a conformation with a potential energy minimum generally coincides with that in the crystal.[8] If the interaction of a drug with the receptor takes place in a low energy form of the molecule, the X-ray crystallographic data could be useful in designing a new drug. Recently compound **6**, which shows a potent bronchodilating activity, has been successfully designed by us[4] on the basis of the X-ray crystallographic data for isoproterenol.

In this paper, we wish to report the synthesis and biological activity of eight compounds (**7a—h**) which involve phenyl, 3,4-dimethoxyphenyl, 2-naphthyl and 1-naphthyl as the aryl

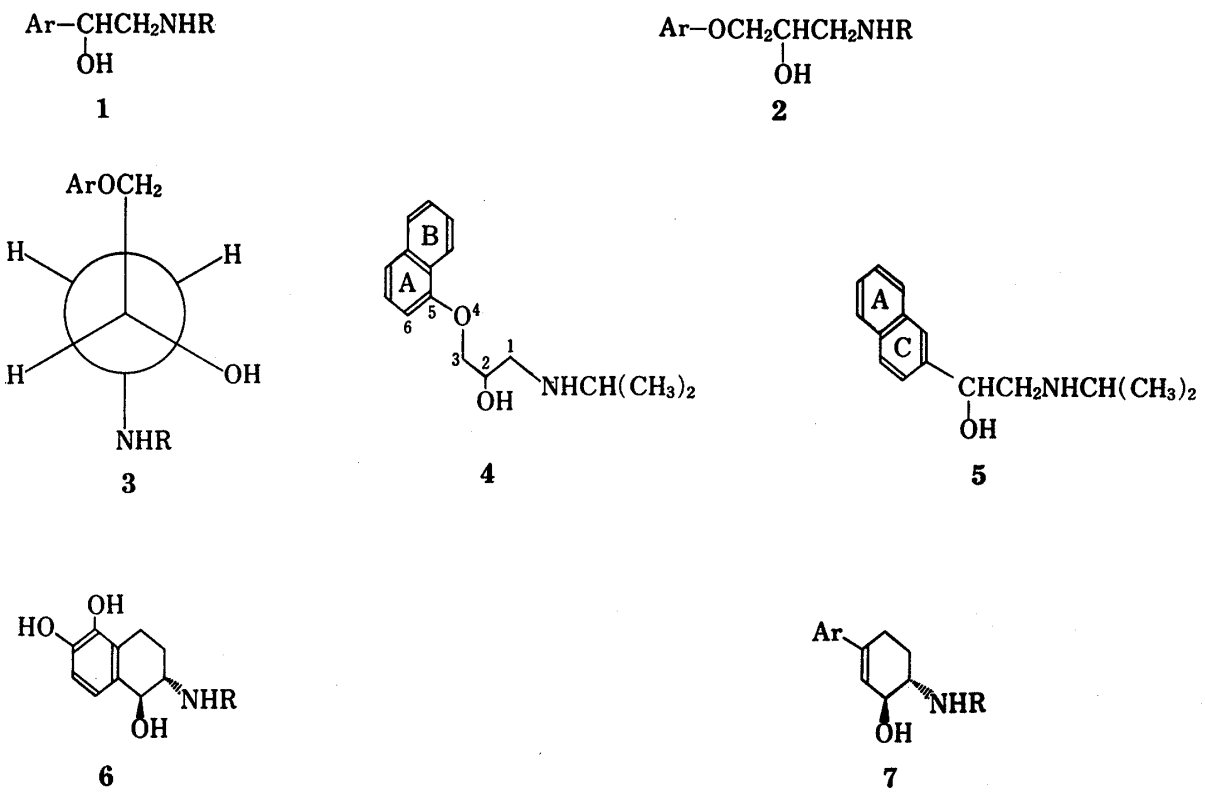


Fig. 1

group and isopropyl and 1-methyl-3-phenylpropyl as the nitrogen substituent.

Chemistry

3-Arylcyclohex-2-enone derivatives (**8a**—**d**) prepared by three-step reactions from the corresponding aryl methyl ketones[5] were employed as the starting materials. Compounds **8a**—**d** were led to 3-arylcyclohex-2-enone *O*-tosyloximes (**10a**—**d**) by reaction with hydroxylamine to afford the oximes (**9a**—**d**), followed by treatment with tosyl chloride in pyridine. The Neber reaction of **10a**—**d**[9] with potassium ethoxide yielded crude 3-aryl-6-aminocyclohex-2-enones contaminated with a considerable amount of by-products.[6] Therefore, the reaction mixture was treated with acetic anhydride and the desired products were isolated as crystalline 3-aryl-6-acetamidocyclohex-2-enones (**11a**—**d**) in 18—23% yields. Reduction of **11a**—**d** with sodium borohydride gave 3-aryl-6-acetamidocyclohex-2-enols (**12a**—**d**), which were led to 3-aryl-6-aminocyclohex-2-enol derivatives (**13a**—**d**) by alkaline hydrolysis.

In the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **13a**—**d**, the proton at the 1-position was observed as a doublet at δ 4.3—4.4 with a coupling constant (J) of 7.5—8.0 Hz. Since the cyclohexene ring of **13** is considered to take a half-chair form by analogy with the tetrahydronaphthalene series,[4,7] this high value of coupling constant indicates the *trans*-diequatorial configuration of the aminoethanol moiety of **13**. The reductive alkylation of **13a**—**d** with acetone and benzylacetone in the presence of sodium cyanoborohydride afforded *trans*-3-aryl-6-isopropylaminocyclohex-2-enols (**7a**—**d**) and *trans*-3-aryl-6-(1-methyl-3-phenylpropyl)aminocyclohex-2-enols (**7e**—**h**), respectively. *trans*-6-Isopropylamino-3-phenylcyclohex-2-enol (**7a**) was converted to the saturated derivative, *trans*-6-isopropylamino-3-phenylcyclohexanol (**14a**), by catalytic hydrogenation.

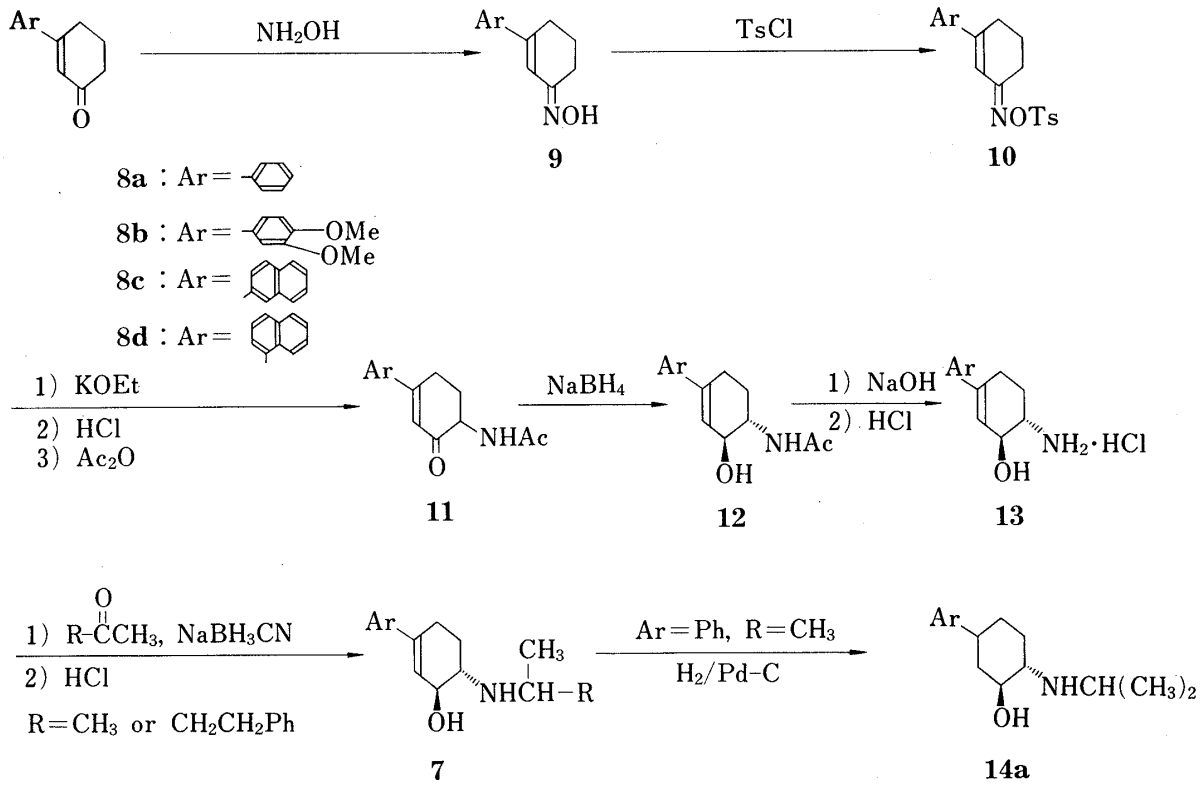
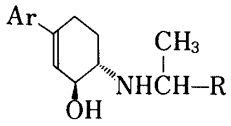
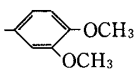
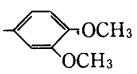


Chart 1

TABLE I. *trans*-3-Aryl-6-aminocyclohex-2-enol Derivatives (**7**)



Compd. No.	Ar	R	Yield (%)	Form	mp (°C) (dec.)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (d_6-DMSO) C_1-H $\delta(J)^{a)}$
7a		CH_3	59	HCl	199—201	$C_{15}H_{21}NO\cdot$ HCl	67.27 (66.81	8.28 8.59	5.23 5.18)	4.50 (7)
7b		CH_3	58	HCl	151—154	$C_{17}H_{25}NO_3\cdot$ HCl	62.28 (61.97	7.99 7.99	4.27 4.36)	4.45 (8)
7c		CH_3	87	HCl	201—202	$C_{19}H_{23}NO\cdot$ HCl	71.79 (71.40	7.61 7.52	4.41 4.46)	4.55 (7)
7d		CH_3	72	HCl	251—252	$C_{19}H_{23}NO\cdot$ HCl	71.79 (71.71	7.61 7.73	4.41 4.33)	4.55 (7)
7e		$(CH_2)_2$- 	71	HCl	173—175	$C_{22}H_{27}NO\cdot$ HCl	73.82 (73.66	7.89 7.79	3.91 3.93)	4.50 (7)
7f		$(CH_2)_2$- 	57	HCl	168—172	$C_{24}H_{31}NO_3\cdot$ HCl	68.96 (68.53	7.72 7.58	3.35 3.34)	4.50 (8)
7g		$(CH_2)_2$- 	81	HCl	186—189	$C_{26}H_{29}NO\cdot$ HCl	76.54 (76.20	7.41 7.33	3.43 3.55)	4.45 (7.5)
7h		$(CH_2)_2$- 	52	HCl	219—221	$C_{26}H_{29}NO\cdot$ HCl	76.54 (76.42	7.41 7.37	3.43 3.40)	4.60 (7)

a) Coupling constants (J) are expressed in Hz.

Biological Results

The compounds were tested for β-adrenergic blocking and antihypertensive activities. The results are listed in Table II. β-Adrenergic blocking activities of **7** were measured *in vitro* with guinea pig atrial preparations in terms of the antagonistic activities to the increase in the beating rate produced by isoproterenol (2.5×10^{-8} M). Two compounds, **7a** and **7e**, were found to have β-antagonistic activity similar to that of practolol, while the rest of the compounds (**7b—d**, **7f—h** and **14a**) were substantially devoid of β-blocking activity. Most of the compounds had no direct cardiac action, but one compound (**7a**) produced an increase in beating rate by about 20%. In the antihypertensive tests of **7** in spontaneously hypertensive rats (SHR), most of the compounds exhibited no significant activity, as was the case with practolol or propranolol. However, **7b** showed a weak hypotensive effect.

TABLE II. Biological Activity

Compd. No.	β-Activity (10^{-6} M)		SHR blood pressure (Δ mmHg)			
	Change in beating rate (%)	Inhibition of isop. (2.5×10^{-8} M) induced tachycardia (%)	Dose (mg/kg)	Control (mmHg)	1 h	3 h
7a	+21.7±1.7	−30.1±5.7	30	186±9	+10±2	+3.7±9
7b	− 4.1±0.9	+18.9±10.0	30	193±6	−23±3[a]	−10±2[a]
7c	− 2.5±0.7	+11.2±5.7	30	199±1	0±8	− 7±5
7d	− 7.5±1.3	− 2.3±8.9	100	204±3	—	− 3±10
7e	+ 0.2±3.2	−32.8±17.1	30	214±20	+14±12	—
7f	− 6.3±1.7	+14.8±3.7	100	209±4	—	−15±5
7g	− 0.4±5.0	+10.9±7.2	30	194±11	−12±5	− 9±8
7h	—	—	30	197±3	− 5±5	− 5±6
14a	− 0.7±0.4	− 5.8±2.8	30	184±14	+11±7	0±16
Practolol	+ 3.2±3.5	−34.2±14.6	30	—	+ 5	+ 7
Propranolol	− 5.8±1.3	−74.9±8.5	30	—	− 3	− 6

a) $p<0.05$ in Student's t-test.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus (a hot stage type) and are uncorrected. The infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer. The ^{1}H-NMR spectra were recorded with a Varian T-60, HA-100 or EM 390 spectrometer with tetramethylsilane (TMS) as an internal standard. The mass spectra (MS) were measured with a Hitachi RMU-6D or RMS-4 mass spectrometer.

3-Arylcyclohex-2-enone (8)——3-Phenylcyclohex-2-enone (**8a**),[5a] 3-(2-naphthyl)cyclohex-2-enone (**8c**)[5b] and 3-(1-naphthyl)cyclohex-2-enone (**8d**)[5b] were prepared according to the procedures in the cited references. 3-(3,4-Dimethoxy)cyclohex-2-enone (**8b**) was obtained in 57% overall yield from 3,4-dimethoxyacetophenone by a procedure similar to that described for **8a**. **8b**, mp 119—120°C. *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.16; H, 6.94. IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.8 (6H, m, methylene protons), 3.9 (6H, s, methoxy protons), 6.4 (1H, s, vinyl proton), 6.8—7.2 (3H, m, phenyl protons).

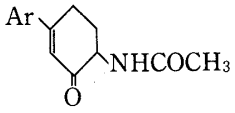
3-Arylcyclohex-2-enone Oxime (9)——A solution of $NH_2OH\cdot HCl$ (15 g) and K_2CO_3 (30 g) in EtOH (100 ml) and water (10 ml) was added to a solution of **8** (10 g), and the mixture was refluxed for 1 h with stirring, then cooled. Water (500 ml) was added and the mixture was extracted with AcOEt (200 ml). The extract was washed with water (50 ml), dried over Na_2SO_4 and concentrated to give **9**. 3-Phenylcyclohex-2-enone oxime (**9a**), colorless prisms (quantitative yield), mp 80—90°C (from petroleum ether). IR ν_{max}^{Nujol} cm^{-1}: 3200 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.2 (2H, m, methylene protons), 2.4—2.9 (4H, m, methylene protons), 6.7 (1H, s, vinyl proton), 7.3—7.7 (5H, m, phenyl protons). *Anal.* Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.94; H, 7.17; N, 7.34. 3-(3,4-Dimethoxyphenyl)cyclohex-2-enone oxime (**9b**), colorless prisms (99%), mp 132—140°C (from ether–petroleum ether). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.88; H, 6.96; N, 5.46. 3-(2-Naphthyl)cyclohex-2-enone oxime (**9c**), oil (90%). IR ν_{max}^{neat} cm^{-1}: 3200, 3300 (OH). 3-(1-Naphthyl)cyclohex-2-enone oxime (**9d**), oil (94%). IR ν_{max}^{neat} cm^{-1}: 3200 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.2 (2H, m, methylene protons), 2.3—2.9 (4H, m, methylene protons),

6.3 (1H, s, vinyl proton), 7.2—8.0 (7H, m, naphthyl protons).

3-Arylcyclohex-2-enone *O*-Tosyloxime (10)——Tosyl chloride (20 g) was added portionwise to an ice-cooled solution of **9** (10 g) in pyridine (100 ml) with stirring. After being stirred for 1 h under ice cooling and for 30 min at room temperature, the mixture was poured into water (500 ml) and extracted with benzene (500 ml). After successive washings with 5% HCl (100 ml × 2), saturated $NaHCO_3$ solution (50 ml) and water (50 ml), the extract was dried over Na_2SO_4 and evaporated to dryness to give **10**. 3-Phenylcyclohex-2-enone *O*-tosyloxime (**10a**), pale yellow viscous oil (97%). IR ν_{max}^{neat} cm^{-1}: 1190, 1180 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.2 (2H, m, methylene protons), 2.4 (3H, s, methyl protons), 2.3—2.9 (4H, m, methylene protons), 6.5 (1H, s, vinyl proton), 7.3—8.1 (9H, m, phenyl protons). 3-(3,4-Dimethoxyphenyl)cyclohex-2-enone *O*-tosyloxime (**10b**), colorless prisms (69%), mp 116—125°C (from $CHCl_3$–EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1190 (SO_2). *Anal.* Calcd for $C_{21}H_{23}NO_5S$: C, 62.83; H, 5.78; N, 3.48. Found: C, 62.55; H, 5.66; N, 3.47. 3-(2-Naphthyl)-cyclohex-2-enone *O*-tosyloxime (**10c**), colorless prisms (94%), mp 117—122°C (from $CHCl_3$–EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1200 (SO_2). *Anal.* Calcd for $C_{23}H_{21}NO_3S$: C, 70.57; H, 5.41; N, 3.58. Found: C, 70.23; H, 5.30; N, 3.51. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.1 (2H, m, methylene protons), 2.4 (3H, s, methyl protons), 2.6—2.8 (4H, m, methylene protons), 6.6 (1H, s, vinyl proton), 7.2—8.0 (11H, m, aryl protons). 3-(1-Naphthyl)-cyclohex-2-enone *O*-tosyloxime (**10d**), pale yellow viscous oil (94%). IR ν_{max}^{neat} cm^{-1}: 1190, 1200 (SO_2). ^{1}H-NMR($CDCl_3$) δ: 1.8—2.3 (2H, m, methylene protons), 2.4 (3H, s, methyl protons), 2.4—2.9 (4H, m, methylene protons), 6.3 (1H, s, vinyl proton), 7.1—7.9 (11H, m, aryl protons).

3-Aryl-6-acetamidocyclohex-2-enone (11, Table III)——A solution of EtOK, prepared from K (0.05 mol) and abs. EtOH (40 ml), was added dropwise to an ice-cooled mixture of **10** (0.05 mol) and dry benzene (300 ml) under N_2. After stirring for 30 min under cooling, the mixture was allowed to stand in a refrigerator for 1 week. The insoluble substance was removed by filtration and conc. HCl (20 ml) and water (20 ml) were added to the filtrate. The aqueous layer was separated and the benzene layer was extracted with 10% HCl (50 ml × 3). AcOEt (150 ml) and Ac_2O (20 ml) was added to the combined aqueous layer, then $NaHCO_3$ (excess) was added portionwise under vigorous stirring to the cooled mixture. The organic layer was separated, dried (Na_2SO_4) and concentrated to give **11** as colorless crystals.

TABLE III. 3-Aryl-6-acetamidocyclohex-2-enones (**11**)



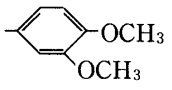
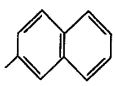
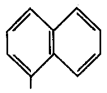
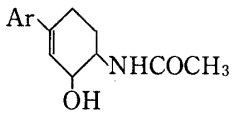
Compd. No.	Ar	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{Nujol} (cm^{-1})	^{1}H-NMR ($CDCl_3$+D_2O) δ
11a		18	137—138	$C_{14}H_{15}NO_2$	73.34 (73.09	6.59 6.55	6.11 6.05)	3380 (NH) 1690 1650 (C=O)	1.7—2.0, 2.7—3.1 (4H, m), 2.05 (3H, s), 4.3—4.7 (1H, m), 6.45 (1H, d, J=1.5 Hz), 7.3—7.6 (5H, m).
11b		18	173—174	$C_{16}H_{19}NO_4$	66.42 (66.26	6.62 6.58	4.84 4.78)	3350 (NH) 1670 1640 (C=O)	1.7—2.0, 2.7—3.1 (4H, m), 2.05 (3H, s), 3.9 (6H, s), 4.3—4.7 (1H, m), 6.4 (1H, s), 6.8—7.3 (3H, m)
11c		23	166—168	$C_{18}H_{17}NO_2$	77.39 (77.54	6.13 6.12	5.01 4.98)	3320 (NH) 1660 1640 (C=O)	1.6—2.0, 2.7—3.2 (4H, m), 2.05 (3H, s), 4.4—4.7 (1H, m), 6.6 (1H, s) 7.6—8.0 (7H, m)
11d		19	159—161	$C_{18}H_{17}NO_2$	77.39 (77.55	6.13 6.02	5.01 4.82)	3300 (NH) 1670 1630 (C=O)	1.95 (3H, s), 2.1—3.3 (4H, m), 4.4—4.8 (1H, m), 6.0 (1H, d, J= 1.5Hz) 7.3—8.0 (7H, m

TABLE IV. 3-Aryl-6-acetamidocyclohex-2-enols (**12**)



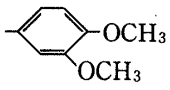
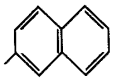
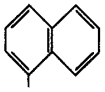
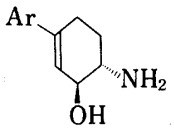
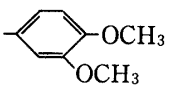
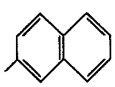
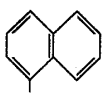
Compd. No.	Ar	Yield (%)	mp (°C) (Rec. sol.)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{Nujol} (cm^{-1})	^{1}H-NMR ($CDCl_3$+D_2O) δ
12a		93	148—150 (MeOH-H_2O)	$C_{14}H_{17}NO_2$	72.70 (72.54	7.41 7.35	6.06 6.00)	3470 3270 (NH,OH) 1640 (C=O)	2.0(3H, s), 1.5—2.3. 2.5—2.7(4H, m), 3.7—4.3(2H, m), 7.2—7.5 (5H, m)
12b		99	144—146 (AcOEt)	$C_{16}H_{21}NO_4$	65.95 (65.82	7.27 7.38	4.81 4.82)	3450 3270 (NH,OH) 1640 (C=O)	2.0(3H, s), 1.5—2.3, 2.4—2.7(4H, m),3.8 (6H, s), 3.7—4.3(2H, m), 5.9(1H, s) 6.7—7.0(3H, m)
12c		97	190—193 ($CHCl_3$)	$C_{18}H_{19}NO_2$	76.84 (76.76	6.81 6.71	4.98 4.83)	3450 3250 (NH,OH) 1640 (C=O)	2.05(3H, s), 1.7—2.3, 2.6—2.8(4H, m), 3.7—4.3(2H, m), 6.2(1H s), 7.3—7.9(7H, m)
12d		95	174—176 (AcOEt)	$C_{18}H_{19}NO_2$	76.84 (76.39	6.81 6.67	4.98 4.82)	3300 (NH,OH) 1640 (C=O)	2.05(3H, s), 1.7—2.3, 2.4—2.7(4H, m), 3.8—4.4(2H, m), 5.7(1H, s) 7.2—8.0(7H, m).

TABLE V. *trans*-3-Aryl-6-aminocyclohex-2-enols (**13**)



Compd. No.	Ar	Yield (%) (Form)	mp (°C) (Rec. sol.)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{Nujol} (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (C_1-H)
13a		43 (HCl)	237—239 (MeOH-Et_2O)	$C_{12}H_{15}NO\cdot$ HCl	63.85 (63.86	7.15 7.30	6.21 6.16)	3300 (OH) 1610 (C=C)	4.35 (d, J=8Hz)
13b		67 (HCl)	206—208 (MeOH-AcOEt)	$C_{14}H_{19}NO_3\cdot$ HCl	58.83 (59.06	7.05 7.09	4.90 5.02)	3260 (OH) 1620 (C=C)	4.30 (d, J=7.5Hz)
13c		81 (HCl)	244—245 (MeOH-AcOEt)	$C_{16}H_{17}NO\cdot$ HCl	69.67 (69.74	6.58 6.45	5.08 4.87)	3300 (OH) 1640 (C=C)	4.40 (d, J=8Hz)
13d		75 (HCl)	243—245 (EtOH-AcOEt)	$C_{16}H_{17}NO\cdot$ HCl	69.67 (69.47	6.58 6.68	5.08 5.08)	3320 (OH) 1620 (C=C)	4.40 (d, J=8Hz)

3-Aryl-6-acetamidocyclohex-2-enol (12, Table IV)——$NaBH_4$ (2.5 g) was added portionwise to a stirred solution of **11** (5 g) in MeOH (50 ml) at room temperature. After being stirred for a further 10 min, the mixture was poured into water (300 ml) and extracted with $CHCl_3$ (50 ml × 3). The extract was dried over Na_2SO_4 and concentrated. The residue (**12**) was recrystallized from an appropriate solvent (Table IV).

***trans*-3-Aryl-6-aminocyclohex-2-enol (13, Table V)**——A mixture of **12** (5 g), EtOH (100 ml) and 10% NaOH (50 ml) was heated at 70—80°C for 20 h. After addition of 500 ml of water, the reaction mixture was extracted with $CHCl_3$ (100 ml × 5). The extract was washed, dried (Na_2SO_4) and concentrated, then 7 N HCl–EtOH (10 ml) was added to the residue and the resulting solution was diluted with ether to deposit crystals of **13**·HCl.

***trans*-6-(*N*-Substituted amino)-3-arylcyclohex-2-enol (7, Table I)**——$NaBH_3CN$ (1.2 g) was added portionwise to a stirred solution of **13**·HCl (1 g) in a mixture of acetone (10 ml) and MeOH (20 ml). After standing for 3 d at room temperature, the reaction mixture was acidified with 10% HCl, poured into water (200 ml), neutralized with $NaHCO_3$, and then extracted with $CHCl_3$ (50 ml × 4). The extract was dried (Na_2SO_4) and concentrated, then 10% HCl–EtOH (10 ml) was added to the residue and the resulting solution was diluted with ether to precipitate **7a—d**·HCl as colorless prisms. Similar procedures were applied for the preparation of **7e—h** using **13**·HCl, benzylacetone and $NaBH_3CN$.

2-Isopropylamino-5-phenylcyclohexanol (14a)——A solution of 6-isopropylamino-3-phenylcyclohex-2-enol hydrochloride (**7a** · HCl, 0.5 g) in MeOH (100 ml) was catalytically hydrogenated over 10% Pd-C (0.5 g) under atmospheric pressure at room temperature until absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was evaporated to dryness. The residue was crystallized from ether to give **14a**·HCl (0.4 g, 79%) as colorless prisms, mp 222—227°C (dec.). *Anal.* Calcd for $C_{15}H_{23}NO \cdot HCl \cdot 1/2H_2O$: C, 64.62; H, 9.04; N, 5.02. Found: C, 65.05; H, 9.03; N, 4.92. IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH).

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6) In the case of the 3-(1-naphthyl) compound, one of the by-products was proved to be the 2-amino ketone isomer, which was isolated as 2-acetylamino-3-(1-naphthyl)cyclohex-2-enone; its ^{1}H-NMR spectrum showed no signal corresponding to the vinyl proton.
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9) We have no evidence at the moment as to whether compounds **9** and **10** consist of a single stereoisomer or a mixture of the *E* and *Z* isomers, although the ^{1}H-NMR spectra of some of the oxime and *O*-tosyloxime derivatives, **9a**, **9d**, **10a**, **10c** and **10d**, showed a singlet corresponding to the vinyl proton. The *O*-tosyloximes **10** were used for the Neber rearrangement without further characterization of the stereochemistry.