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Studies on 1,2,3,4-Tetrahydroisoquinolines. II.[1] A One-pot Synthesis of 1-Arylmethyl-1,2,3,4-tetrahydroisoquinolines from an Isoquinolinium Salt[2]

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In connection with our previous study on the β-adrenoceptor activities of the positional isomers of trimetoquinol, various 1-arylmethyl-1,2,3,4-tetrahydroisoquinolines (**10b—i**) were synthesized. The Barbier reaction of the quaternary salt (**7**) with arylmethyl halides, followed by sodium monoacetoxyborohydride [$NaBH_3(OAc)$] reduction in a one-pot procedure, gave the tribenzyltetrahydroisoquinolines (**9b—i**) in excellent yields. Catalytic debenzylation of **9b—i** furnished **10b—i**. None of the compounds (**10b—i**) exhibited significant bronchodilating activity.

Keywords——1-arylmethyl-1,2,3,4-tetrahydroisoquinoline; one-pot synthesis; Barbier reaction; sodium monoacetoxyborohydride reduction; trimetoquinol; bronchodilator; intravenous administration; structure–activity relationship

In the preceding paper,[1] we reported the syntheses and β-adrenoceptor activities of the five positional isomers of trimetoquinol (TMQ) with respect to its 6,7-dihydroxyl groups. The 5,7-dihydroxy derivative **1** showed more potent activity and longer duration of action than (±)-TMQ on intraduodenal administration (Chart 1). This finding prompted us to carry out the structural modification of **1** by replacing the 3,4,5-trimethoxybenzyl group at the 1-position with other arylmethyl groups.

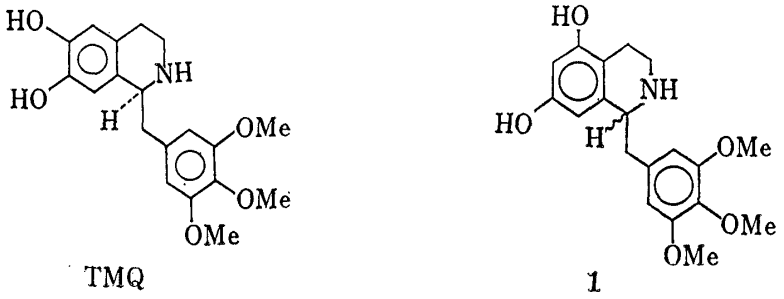

Chart 1

Previously,[1] compound **1** was prepared from the isoquinoline **2** *via* the Reissert compound **3** in several steps in 40% overall yield (Chart 2). During the course of our study on a more convenient synthetic route to the derivatives of **1**, we investigated a one-pot synthesis of 1-arylmethyl-1,2,3,4-tetrahydroisoquinolines **9a—i** by the Barbier reaction[3] of the quaternary salt **7** with arylmethyl halides followed by reduction with sodium monoacetoxyborohydride (Chart 3).

In 1954, Bradley and Jeffrey[4] reported that the addition of alkyl Grignard reagents to 2-alkylisoquinolinium salts gave 1-alkylated 1,2-dihydroisoquinoline derivatives. As is well known, however, reaction of arylmethyl halides with magnesium under the usual conditions tends to produce Wurtz-type condensation products.[5] For instance, the reaction of 3,4,5-trimethoxybenzyl chloride **4** with magnesium[6] in tetrahydrofuran at room temperature for 1 h followed by quenching the Grignard mixture with carbon dioxide gave the phenylacetic

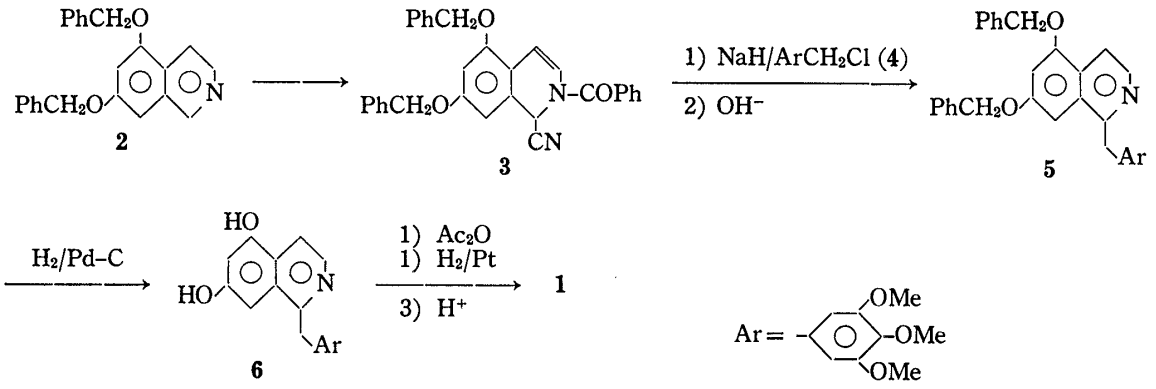

Chart 2

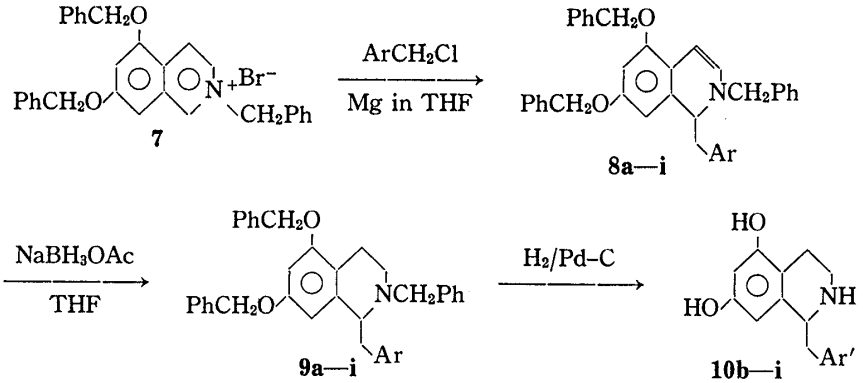

Chart 3

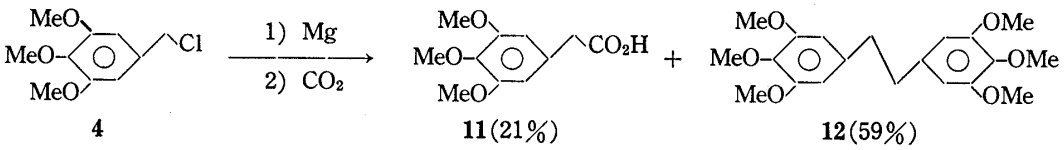

Chart 4

acid **11** (mp 116—118 °C) in only 21% yield, the dimer **12** (mp 138—139 °C) being the major product (59%) (Chart 4). Therefore, we examined the Barbier reaction of the quaternary salt **7** with the halide **4** in order to minimize the formation of the dimer **12.**

Treatment of **4** (1.4 mmol) with magnesium (1.5 mg-atom) in refluxing tetrahydrofuran in the presence of **7** (1 mmol) gave the 1,2-dihydroisoquinoline **8a** in excellent yield. Without purification, **8a** was reduced by treatment with sodium borohydride (15 mmol) in refluxing MeOH containing a small amount of water, or by catalytic hydrogenation on PtO_2 in tetrahydrofuran to afford the tetrahydroisoquinoline **9a**[1] in 83% or 73% yield (from **7**) (Chart 5). Thus, the Barbier method was found to be greatly superior to the Grignard method for the preparation of 1-arylmethyl-1,2,3,4-tetrahydroisoquinolines.

Next, we examined direct reduction of the intermediate 1,2-dihydroisoquinoline **8a** with metal hydride without isolation. Recently, we reported that sodium monoacyloxyborohydride ($NaBH_3OCOR$) effectively reduces various functional groups (*e.g.* carboxamides, carbamates, or nitriles) to the corresponding amines in a non-hydroxylic solvent such as tetrahydrofuran or dioxane.[7] Thus, the tetrahydrofuran solution of the Barbier mixture containing the intermediate **8a** was treated with 6 equiv. of sodium monoacetoxyborohydride under reflux for 1 h to afford the tetrahydroisoquinoline **9a** in 92% yield (from **7**). By applying this new one-pot synthesis of 1-arylmethyl-1,2,3,4-tetrahydroisoquinolines, **9b—i** bearing

various arylmethyl groups at the 1-position were prepared in excellent yields. The results are summarized in Table I.

Finally, catalytic debenzylation of the tetrahydroisoquinolines **9b—i** on 10% Pd–C gave the 5,7-dihydroxy derivatives **10b—i** in high yields. The results are listed in Table II.

The bronchodilating activities of 1-arylmethyl-5,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines **10b—i** thus obtained were tested in anesthetized cats using the methods described in the

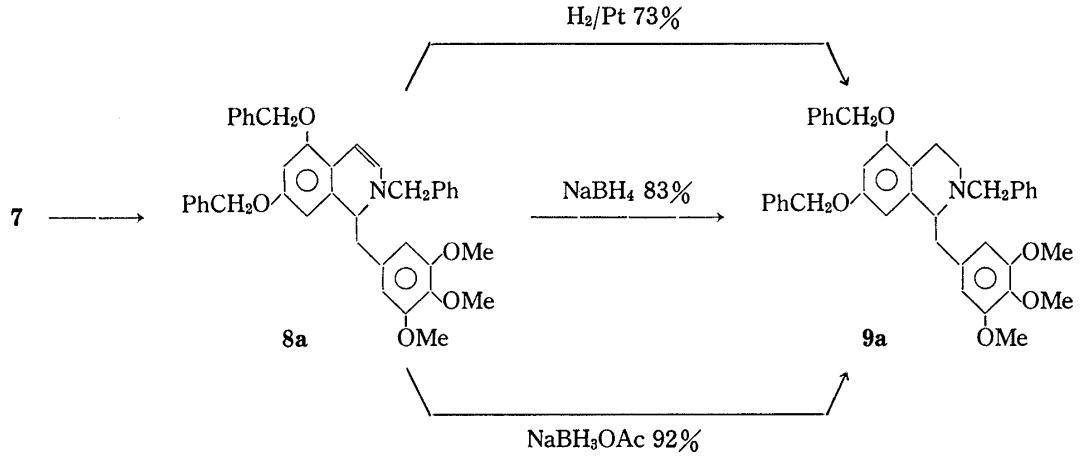

Chart 5

TABLE I. Barbier Reaction of the Quaternary Salt (**7**) with Various Arylmethyl Halides followed by Reduction with Sodium Monoacetoxyborohydride

Compd.	Ar	Salt	Yield (%)	mp (°C) (dec.)	Recrystn.[a] solvent	Formula	Analysis (%) Calcd (Found) C	H	N
9a	3,4,5-(MeO)₃C₆H₂-	HCl	92	132—136	A-B	$C_{40}H_{41}NO_5 \cdot HCl \cdot 1/2H_2O$	72.66 (72.39)	6.55 (6.80)	2.12 (2.11)
9b	4-MeOC₆H₄-	Oxalate	86	171—172	A-B	$C_{38}H_{35}NO_3 \cdot (CO_2H)_2$	74.63 (74.22)	5.79 (6.16)	2.17 (1.99)
9c	3,4-(MeO)₂C₆H₃-	Oxalate	86	154—156	A-B	$C_{39}H_{39}NO_4 \cdot (CO_2H)_2 \cdot 1/2MeOH$	72.05 (71.92)	6.27 (6.13)	2.02 (1.84)
9d	2,3,4-(MeO)₃C₆H₂-	Oxalate	83	122—125	A-B	$C_{40}H_{41}NO_5 \cdot (CO_2H)_2$	71.47 (71.44)	6.14 (6.28)	1.98 (1.87)
9e	2-PhCH₂O-3-MeOC₆H₃-	Oxalate	84	185—187	A-B	$C_{45}H_{43}NO_4 \cdot (CO_2H)_2$	75.08 (74.61)	6.03 (6.03)	1.79 (1.79)
9f	2-PhCH₂O-3-MeOC₆H₃-	Oxalate	88	185—186	A-B-C	$C_{45}H_{43}NO_4 \cdot (CO_2H)_2$	75.08 (74.90)	6.03 (6.04)	1.79 (1.70)
9g	2,3-(PhCH₂O)₂C₆H₃-	Oxalate	89	171—172	A-B-D	$C_{51}H_{47}NO_4 \cdot (CO_2H)_2$	76.88 (76.58)	5.97 (6.02)	1.69 (1.55)
9h	2,6-(PhCH₂O)₂C₆H₃-	Oxalate	84	176—177	A-B-D	$C_{51}H_{47}NO_4 \cdot (CO_2H)_2 \cdot 1/2MeOH$	76.13 (76.09)	6.09 (6.04)	1.66 (1.50)
9i	1-Naphthyl-	Oxalate	93	184—185	E	$C_{41}H_{37}NO_2 \cdot (CO_2H)_2$	77.57 (77.47)	5.90 (6.06)	2.10 (2.07)

a) A: MeOH, B: Et_2O, C: AcOEt, D: $CHCl_3$, E: EtOH.

Table II. 1-Arylmethyl-5,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines **10b—i**

Compd.	Ar′	Salt	Yield (%)	mp (°C) (dec.)	Recrystn.[a] Solvent	Formula	Analysis (%) Calcd (Found) C	H	N
10b	3-MeO	HCl	93	259—261	A-B	$C_{17}H_{19}NO_3 \cdot HCl$	63.45 (63.34	6.24 6.13	4.35 4.38)
10c	3,4-(MeO)$_2$	Oxalate	95	234—235	A-B-C	$C_{18}H_{21}NO_4 \cdot 1/2(CO_2H)_2 \cdot H_2O$	60.31 (60.63	6.39 6.64	3.70 3.72)
10d	3,4,5-(MeO)$_3$	HCl	96	236—237	A-B	$C_{19}H_{23}NO_5 \cdot HCl$	59.76 (59.52	6.34 6.44	3.67 3.86)
10e	4-HO-3-MeO	HCl	81	267—268	A-B-C	$C_{17}H_{19}NO_4 \cdot HCl \cdot H_2O$	57.38 (57.49	6.23 6.25	3.94 3.93)
10f	4-HO-3-MeO	Oxalate	65	271—273	A-B-C	$C_{17}H_{19}NO_4 \cdot 1/2(CO_2H)_2 \cdot 1/2H_2O$	60.83 (61.17	5.96 5.75	3.94 3.89)
10g	3,4-(HO)$_2$	HCl	91	300—302	B-C-D	$C_{16}H_{17}NO_4 \cdot HCl \cdot 3/4H_2O$	56.98 (57.10	5.83 5.89	4.15 4.21)
10h	3,4-(HO)$_2$	Oxalate	64	262—263	B-C-D	$C_{16}H_{17}NO_4 \cdot 1/2(CO_2H)_2 \cdot 3/4H_2O$	59.05 (58.71	5.47 5.13	4.05 3.97)
10i	1-naphthyl	HCl	90	232—233	B-D	$C_{20}H_{19}NO_2 \cdot HCl \cdot H_2O$	66.76 (66.61	6.16 6.06	3.89 3.80)

a) A: MeOH, B: Et_2O, C: H_2O, D: EtOH.

Table III. Bronchodilating Activities of **10b—i** after Intravenous Administration in Anesthetized Cats

Compound	Potency ratio
Isoproterenol	1000
(±)-Trimetoquinol	380
1	250
10b	4
10c	37
10d	1.5
10e	2
10f	5
10g	23
10h	<0.1
10i	6

previous paper[1] (*i.v.* administration). None of the compounds (**10b—i**) synthesized in the present study showed significant activity (Table III). Thus, the replacement of the 3,4,5-trimethoxybenzyl group of **1** by other arylmethyl groups resulted in a marked fall in activity. The importance of this moiety in conferring β-adrenoceptor activity thus parallels the reported observation in the 6,7-dihydroxy (TMQ) series.[8,9]

Experimental

Melting points are uncorrected. IR spectra were recorded with a Hitachi IR-215 spectrometer, NMR spectra with a JEOL JNM-60 spectrometer (using TMS as an internal standard), and mass spectra with a Hitachi RMU-6M spectrometer.

Reaction of 3,4,5-Trimethoxybenzyl Chloride 4 with Mg——1,2-Dibromoethane (0.1 ml) was added to a stirred suspension of Mg (0.66 g, 27.2 mg-atom) in THF (30 ml) under N_2 at room temperature. After 15 min, 3,4,5-trimethoxybenzyl chloride **4** (1.50 g, 6.91 mmol) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was quenched with CO_2 at room temperature, then treated with H_2O and extracted with Et_2O. The Et_2O extracts were washed successively with 10% aq. HCl, H_2O, 10% aq. Na_2CO_3, and H_2O, dried (Na_2SO_4), and concentrated to leave the dimer **12** (737 mg, 59%) as a colorless solid, mp 135—138°C, which was recrystallized from EtOH to give colorless prisms, mp 138—139°C (lit.[10] mp 138—139°C). The combined aq. Na_2CO_3 washings were acidified with 10% aq. HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and concentrated to leave **11** (312 mg, 21%) as a colorless solid, mp 112—115°, which was recrystallized from C_6H_6–hexane to give colorless pillars, mp 116—118°C (lit.[11] mp 120°C).

2-Benzyl-5,7-dibenzyloxyisoquinolinium Bromide 7——A mixture of 5,7-dibenzyloxyisoquinoline **2**[1] (16.5 g, 50 mmol) and benzyl bromide (8.8 g, 52 mmol) in C_6H_6 (100 ml) was refluxed for 3 h and then cooled. The resulting precipitates were collected by filtration to give **7** (25.0 g, 97%), mp 115—120°C. Recrystallization from EtOH–AcOEt–Et_2O gave **7**·EtOH as yellow prisms, mp 102—110°C. IR ν_{max}^{Nujol} cm^{-1}: 3400 (br), 1605. NMR ($CDCl_3$) δ: 1.21 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2OH$), 3.70 (2H, q, $J=7$ Hz, $CH_3C\underline{H}_2OH$), 5.21 (4H, s, $-OC\underline{H}_2C_6H_5\times2$), 6.29 (2H, s, $N^+-C\underline{H}_2C_6H_5$), 7.0—7.9 (17H, m), 8.33 and 8.73 (1H each, AB type d's, $J=$ 7 Hz, H (4) and H (3)), 10.97 (1H, s, H(1)). *Anal.* Calcd for $C_{30}H_{26}BrO_2N\cdot EtOH$: C, 68.82; H, 5.78; N, 2.50; Br, 14.31. Found: C, 68.74; H, 5.79; N, 2.47; Br, 14.31.

2-Benzyl-5,7-dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-1,2-dihydroisoquinoline 8a——1,2-Dibromoethane (3 drops) was added to a stirred suspension of Mg (40 mg, 1.5 mg-atom) in THF (10 ml) under N_2 at room temperature. After 15 min, the quaternary salt **7** (513 mg, 1 mmol) was added. A solution of 3,4,5-trimethoxybenzyl chloride (304 mg, 1.4 mmol) in THF (5 ml) was added to this mixture with stirring, and the whole was refluxed for 1 h. The reaction mixture was treated with H_2O and extracted with C_6H_6. The C_6H_6 extracts were washed with sat. brine, dried (Na_2SO_4), and concentrated to leave **8a** (647 mg, quant.) as a pale yellow viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1585, 1565. MS (*m/e*): 613 (M^+). NMR ($CDCl_3$) δ: 3.69, 3.76, and 3.78 (9H, s, OMe×3), 4.16 (2H, s, $NC\underline{H}_2C_6H_5$), 4.70 and 5.00 (2H, each, s, $-OC\underline{H}_2C_6H_5\times2$), 5.68 (1H, d, $J=2$ Hz, H(8)), 5.74 (1H, d, $J=7$ Hz, H (4)), 6.10 (2H, s, H (2′) and H (6′)), 6.13 (1H, d, $J=7$ Hz, H (3)), 6.44 (1H, d, $J=2$ Hz, H (6)), 7.2—7.4 (15H, m, $-C_6H_5\times3$).

Reduction of the 1,2-Dihydroisoquinoline 8a——i) $NaBH_4$ (380 mg, 10 mmol) was added to a mixture of **8a** (647 mg, 1 mmol), MeOH (60 ml), and H_2O (4 ml) and the mixture was refluxed for 30 min, then cooled. $NaBH_4$ (190 mg, 5 mmol) was added and the mixture was again refluxed for 30 min, then allowed to stand at 5—10°C overnight. The resulting precipitates were collected by filtration, washed successively with H_2O and MeOH, and dried to give **9a** (510 mg, 83%) as colorless needles, mp 104—106°C. This material was identical with an authentic sample[1] (IR and NMR spectra and mixed melting point).

ii) A solution of **8a** (0.87 g, 1.35 mmol) in THF (25 ml) was hydrogenated on PtO_2 (0.05 g) at room temperature and at 3.3 times atmospheric pressure for 0.5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was crystallized from MeOH (10 ml) to afford **9a** (605 mg, 73%) as colorless needles, mp 103—104°C.

Barbier Reaction of the Quaternary Salt 7 with Various Arylmethyl Halides followed by Reduction with Sodium Monoacetoxyborohydride (One-pot Procedure) (Table I)——A typical procedure is as follows. 1,2-Dibromoethane (0.8 g) was added to a stirred suspension of Mg (2.2 g, 91 mg-atom) in THF (50 ml) under N_2 at room temperature. After 30 min, the quaternary salt **7** (30.7 g, 60 mmol) and THF (80 ml) were added. A solution of 3,4,5-trimethoxybenzyl chloride **4** (18.2 g, 84 mmol) in THF (40 ml) was then added to the stirred mixture, and the whole was refluxed for 1 h, then cooled. $NaBH_4$ (13.7 g, 0.36 mol) was added to the reaction mixture, and then AcOH (21.6 g, 0.36 mol) was added under ice–water cooling. The whole was gradually heated at reflux for 1 h. The reaction mixture was poured into ice–water and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was treated with 12% methanolic HCl and concentrated *in vacuo* to leave a solid, which was recrystallized from MeOH–Et_2O to afford **9a**·HCl (36.9 g, 92%) as colorless prisms, mp 132—136°C (dec.). This sample was identical with an authentic sample[1] (IR and NMR spectra and mixed melting point).

Hydrogenolysis of the O-Benzyl Derivatives (9b—i) to the Corresponding 5,7-Dihydroxy Isoquinolines (10b—i) (Table II)——A typical procedure is as follows. A mixture of **9c**·oxalate (4.5 g, 6.5 mmol), MeOH (50 ml), and H_2O (5 ml) was hydrogenated on 10% Pd-C (0.6 g) at 50°C and at 3.0 times atmospheric pressure for 1.5 hr. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to leave a colorless solid, which was recrystallized from MeOH–H_2O–Et_2O to give **10c**·oxalate (2.33 g, 95%) as colorless needles, mp 234—235°C (dec.).

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