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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 Salt²⁾

KOICHIRO YAMADA, NOBUO ITOH, KATSUO IKEZAWA, AKIO KIYOMOTO,
and TAKEO IWAKUMA*

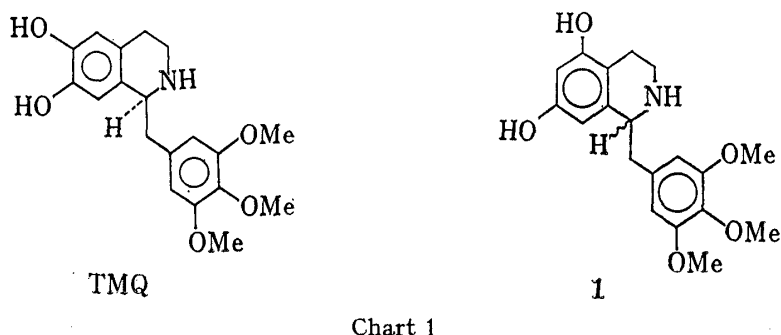
Research Laboratories, Tanabe Seiyaku, Co., Ltd., Kawagishi, Toda-shi, Saitama, Japan

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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 [$\text{NaBH}_3(\text{OAc})$] 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 ($\pm$)-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.



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 reaction³⁾ of the quaternary salt **7** with arylmethyl halides followed by reduction with sodium monoacetoxyborohydride (Chart 3).

In 1954, Bradley and Jeffrey⁴⁾ 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 magnesium⁶⁾ in tetrahydrofuran at room temperature for 1 h followed by quenching the Grignard mixture with carbon dioxide gave the phenylacetic

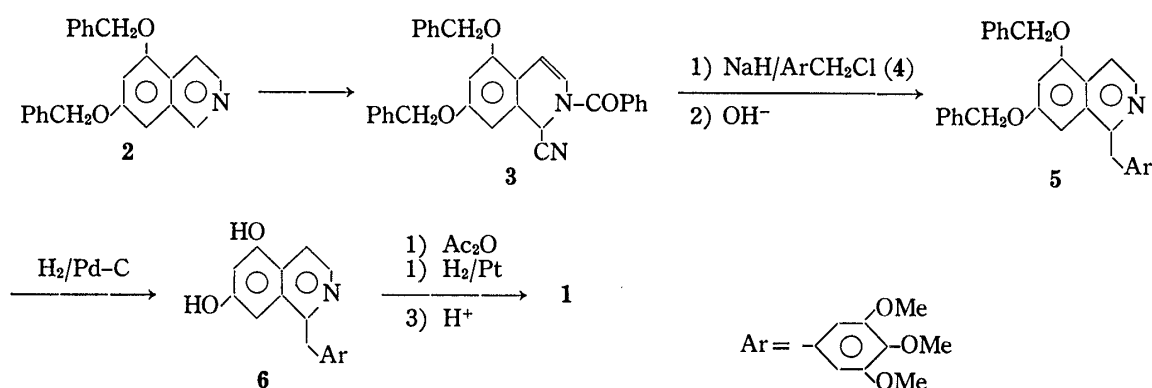


Chart 2

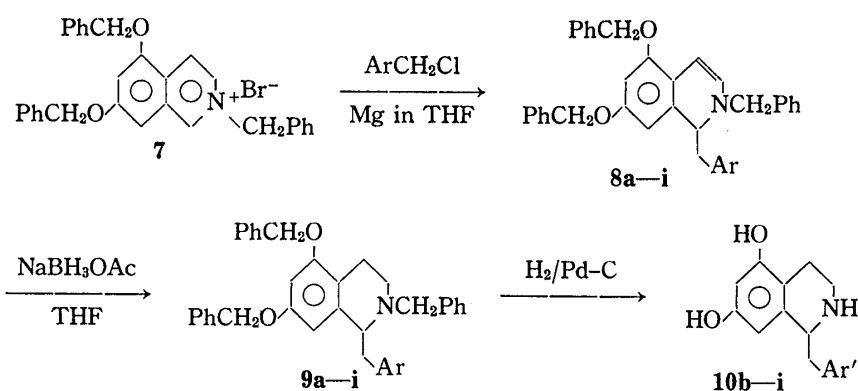


Chart 3

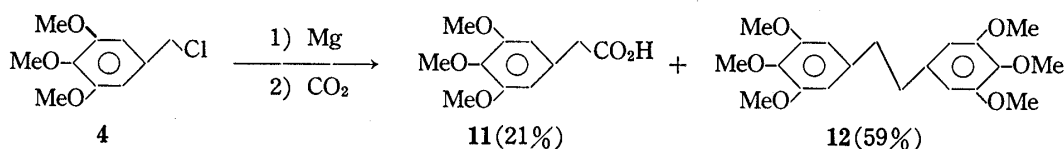


Chart 4

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 PtO₂ 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 (NaBH₃OCOR) 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 debenzoylation 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

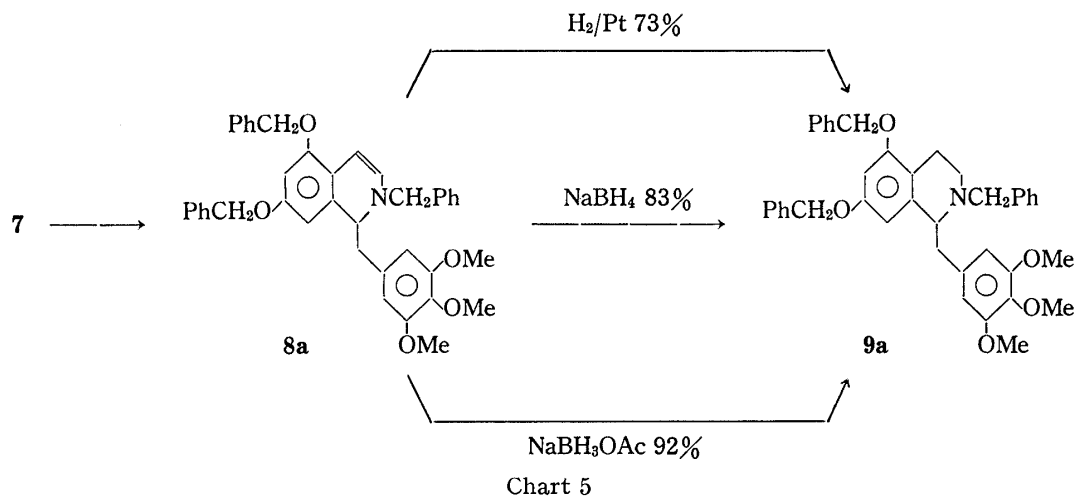
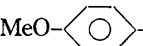
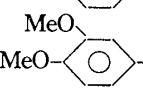
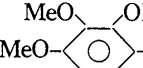
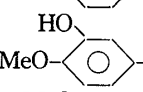
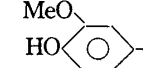
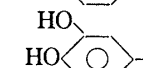
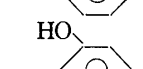
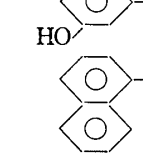


TABLE I. Barbier Reaction of the Quaternary Salt (7) with Various Arylmethyl Halides followed by Reduction with Sodium Monoacetoxyborohydride

Compd.	Ar	Salt	Yield (%)	mp (°C) (dec.)	Recrystn. ^{a)} solvent	Formula	Analysis (%)		
							Calcd (Found)	C	H N
9a		HCl	92	132—136	A—B	C ₄₀ H ₄₁ NO ₅ ·HCl· 1/2H ₂ O	72.66 (72.39)	6.55 6.80	2.12 2.11
9b		Oxalate	86	171—172	A—B	C ₃₈ H ₃₅ NO ₃ ·(CO ₂ H) ₂	74.63 (74.22)	5.79 6.16	2.17 1.99
9c		Oxalate	86	154—156	A—B	C ₃₉ H ₃₉ NO ₄ ·(CO ₂ H) ₂ · 1/2MeOH	72.05 (71.92)	6.27 6.13	2.02 1.84
9d		Oxalate	83	122—125	A—B	C ₄₀ H ₄₁ NO ₅ ·(CO ₂ H) ₂	71.47 (71.44)	6.14 6.28	1.98 1.87
9e		Oxalate	84	185—187	A—B	C ₄₅ H ₄₃ NO ₄ ·(CO ₂ H) ₂	75.08 (74.61)	6.03 6.03	1.79 1.79
9f		Oxalate	88	185—186	A—B—C	C ₄₅ H ₄₃ NO ₄ ·(CO ₂ H) ₂	75.08 (74.90)	6.03 6.04	1.79 1.70
9g		Oxalate	89	171—172	A—B—D	C ₅₁ H ₄₇ NO ₄ ·(CO ₂ H) ₂	76.88 (76.58)	5.97 6.02	1.69 1.55
9h		Oxalate	84	176—177	A—B—D	C ₅₁ H ₄₇ NO ₄ ·(CO ₂ H) ₂ · 1/2MeOH	76.13 (76.09)	6.09 6.04	1.66 1.50
9i		Oxalate	93	184—185	E	C ₄₁ H ₃₇ NO ₂ ·(CO ₂ H) ₂	77.57 (77.47)	5.90 6.06	2.10 2.07

a) A: MeOH, B: Et₂O, C: AcOEt, D: CHCl₃, 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
10b		HCl	93	259—261	A—B	C ₁₇ H ₁₉ NO ₃ ·HCl	63.45 (63.34)	6.24 6.13	4.35 4.38
10c		Oxalate	95	234—235	A—B—C	C ₁₈ H ₂₁ NO ₄ · 1/2(CO ₂ H) ₂ ·H ₂ O	60.31 (60.63)	6.39 6.64	3.70 3.72
10d		HCl	96	236—237	A—B	C ₁₉ H ₂₃ NO ₅ ·HCl	59.76 (59.52)	6.34 6.44	3.67 3.86
10e		HCl	81	267—268	A—B—C	C ₁₇ H ₁₉ NO ₄ ·HCl·H ₂ O	57.38 (57.49)	6.23 6.25	3.94 3.93
10f		Oxalate	65	271—273	A—B—C	C ₁₇ H ₁₉ NO ₄ · 1/2(CO ₂ H) ₂ ·1/2H ₂ O	60.83 (61.17)	5.96 5.75	3.94 3.89
10g		HCl	91	300—302	B—C—D	C ₁₆ H ₁₇ NO ₄ ·HCl· 3/4H ₂ O	56.98 (57.10)	5.83 5.89	4.15 4.21
10h		Oxalate	64	262—263	B—C—D	C ₁₆ H ₁₇ NO ₄ · 1/2(CO ₂ H) ₂ ·3/4H ₂ O	59.05 (58.71)	5.47 5.13	4.05 3.97
10i		HCl	90	232—233	B—D	C ₂₀ H ₁₉ NO ₂ ·HCl·H ₂ O	66.76 (66.61)	6.16 6.06	3.89 3.80

a) A: MeOH, B: Et₂O, C: H₂O, 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 paper¹⁾ (*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 2¹ (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}^{NaCl} cm^{-1} : 3400 (br), 1605. NMR ($CDCl_3$) δ : 1.21 (3H, t, $J=7$ Hz, CH_3CH_2OH), 3.70 (2H, q, $J=7$ Hz, CH_3CH_2OH), 5.21 (4H, s, $-OCH_2C_6H_5 \times 2$), 6.29 (2H, s, $N^+-CH_2C_6H_5$), 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, $OMe \times 3$), 4.16 (2H, s, $NCH_2C_6H_5$), 4.70 and 5.00 (2H, each, s, $-OCH_2C_6H_5 \times 2$), 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, $-C_6H_5 \times 3$).

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 sample¹ (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 sample¹ (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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References and Notes

- 1) Part I: K. Yamada, M. Ikezaki, N. Umino, H. Ohtsuka, N. Itoh, K. Ikezawa, A. Kiyomoto, and T. Iwakuma, *Chem. Pharm. Bull.*, **29**, 744 (1981).
- 2) Preliminary communication: T. Iwakuma, K. Yamada, N. Itoh, and S. Sugasawa, *Heterocycles*, **15**, 1115 (1981).
- 3) For a general review, see C. Bromberg and F.A. Hartog, *Synthesis*, **1977**, 18.
- 4) W. Bradley and S. Jeffrey, *J. Chem. Soc.*, **1954**, 2770.
- 5) A.H. Jackson and G.W. Stewart, *J. Chem. Soc. Perkin I*, **1974**, 1911.
- 6) A catalytic amount of 1,2-dibromoethane was used to activate the metal surface of magnesium. See D.E. Pearson, D. Cowan, and J.D. Beckler, *J. Org. Chem.* **24**, 504 (1959).
- 7) T. Iwakuma, N. Umino, and N. Itoh, *Yuki Gosei Kagaku Kyokai Shi*, **35**, 300 (1977).
- 8) Y. Iwasawa and A. Kiyomoto, *Japan. J. Pharmacol.*, **17**, 143 (1967).
- 9) E. Yamato, M. Hirakura, and S. Sugasawa, *Tetrahedron*, Suppl. **8**, Part I, 129 (1966).
- 10) H. Richtzenhain, *Chem. Ber.*, **77**, 409 (1944).
- 11) A. Kamal, A. Ali Qureshi, A. Ahmad, and R.W. Richards, *Tetrahedron*, **21**, 1411 (1965).