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CONVENIENT PREPARATION OF TACRINE DERIVATIVES BY THE REDUCTION OF 9-AMINOACRIDINES WITH NICKEL-ALUMINUM ALLOY

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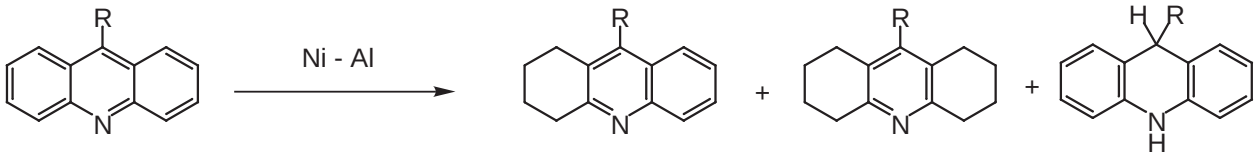
Abstract- 9-Amino-1,2,3,4-tetrahydro- and 9-amino-1,2,3,4,5,6,7,8-octahydro-acridine derivatives (**2** and **3**) were conveniently prepared in the reduction of the corresponding 2-substituted 9-aminoacridines (**1a-f**) with nickel-aluminum alloy under basic conditions. The reduction is dependent upon the nature of the substituent in the 2-position of the starting 9-aminoacridines.

Tacrine (9-amino-1,2,3,4-tetrahydroacridine) acts as the reversible acetylcholine esterase inhibitor and therefore has a potential as a drug for Alzheimer disease.[1] As it suffers a drawback due to long term dose hepatotoxic complications, considerable synthetic efforts were given for searching derivatives with reduced side effects.[2] Partial hydrogenation of 9-aminoacridine affords the method for the construction of fundamental 1,2,3,4-tetrahydroacridine structure, in principle. Selective formation of 9-amino-1,2,3,4-acridine (67% yield at a conversion of 61%) was reported using noble metal catalyst (Pd, Rh, Pt, and Ru) under 60 atom of hydrogen.[3] However, the catalytic hydrogenation of 9-aminoacridine in the presence of Raney nickel catalyst gave 9,10-dihydro derivative under normal pressure.[4]

Treatment of a substrate with Raney aluminum alloy in either acidic or basic media is a convenient method for the reduction of functional groups and aromatic rings.[5] The method for reduction was applied for polynuclear azahetrocycles such as quinolines and isoquinolines to give the benzo[*b*]- and benzo[*c*]-

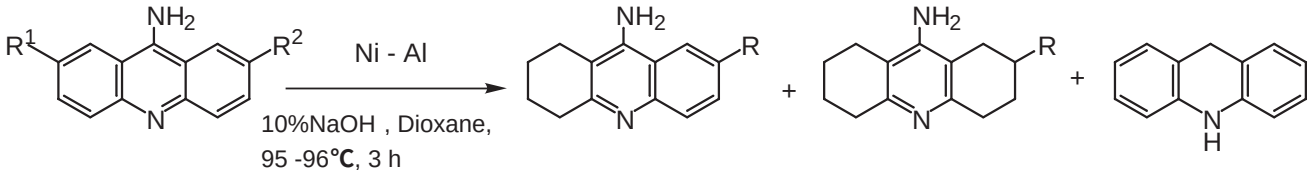
piperidine, respectively.[6] On the other hand, the benzo ring(s) was reduced in the treatment of 9-alkylacridines, giving the corresponding 1,2,3,4-tetrahydro- and 1,2,3,4,5,6,7,8-octahydroacridines.[7]



(R = H, CH_3, C_2H_5, C_3H_7, iso- C_3H_7)

Thus, it seems a reasonable expectation that the reduction of 9-aminoacridines with Raney aluminum alloy in either acidic or basic media gives substituted 9-amino-1,2,3,4-tetrahydroacridines and/or its further hydrogenated derivatives, 9-amino-1,2,3,4,5,6,7,8-octahydroacridines.

The reduction of 9-aminoacridines (**1**) with nickel-aluminum alloy was carried out under basic conditions and 9-amino-1,2,3,4-tetrahydroacridines (**2**) and/or 9-amino-1,2,3,4,5,6,7,8-octahydroacridines (**3**) were obtained (Scheme 1 and Table 1). Sonication improved the yields of **2**. On the other hand, the reduction failed under acidic conditions, although effective in the case of 9-alkylacridines, probably due to the formation of unreactive hydrochloride.



1a - f

2a; R = H , **2d**; R = CH_3 , **2e**; R = OCH_3

3a; R = H , **3f**; R = C_6H_5

4

Scheme 1

Table 1. Reduction of 2-substituted 9-aminoacridines (**1a - f**)

Substrate	R^1	R^2	Product, Yield (%)	
1a	H	H	**2a** (79)	**3a** (trace)**4**(11)
1a[a]	H	H	**2a** (60)	**4** (26)
1b	Br	H	**2a** (8)	**3a** (88)
1c	Br	Br	**2a** (27)	**3a** (63)
1d	CH_3	H	**2d** (76)	
1e	OCH_3	H	**2e** (56)	**3a** (16)
1f	C_6H_5	H	**3f** (57)	

a) Without sonication

1,2,3,4-Tetrahydro-9-aminoacridine (**2a**) was produced in 79% yield in the reduction of **1a**, accompanied by octahydro derivative (**3a**) in a trace amount. In the reduction, the amino group was reductively removed and 9,10-dihydroacridine (**4**) was formed as a by-product in 11% yield. An introduction of bromo atom in the acridine ring was found effective for the formation of octahydro derivatives in the

reduction of 9-alkylacridines. 2-Bromo-9-aminoacridine (**1b**) gave **3a** in 88% yield. Contrary, dibromoaminoacridine (**1c**) gave **3a** in a decreased amount (63%). In the reduction of **1c**, debromination reaction occurred on the aromatic ring to give **2a** in 27% yield.

Alkyl, alkoxy or aryl group on the 2-position of the acridine ring controlled the direction of ring-reduction. In the reduction of 9-amino-2-methylacridine (**1d**), unsubstituted benzo-ring was reduced selectively to give 9-amino-7-methyl-1,2,3,4-tetrahydroacridine (**2d**) in 76% yield. Similarly, methoxyacridine (**1e**) gave 7-methoxy derivative (**2e**). In the reduction, the methoxy group was reductively cleaved and **3a** was given in 16% yield as a minor product. On the other hand, the reduction of **1f** gave 2-phenyloctahydro derivative (**3f**) in 57% yield. π-Electrons of the phenyl group may work favorable for the contact of the substrate on the hydrogen-absorbed nickel surface.[8]

9-Amino-1,2,3,4-tetra- (**2**) and/or 9-amino-1,2,3,4,5,6,7,8-octahydroacridines (**3**) were obtained by the reduction of the benzo ring(s) of 2-substituted-9-aminoacridines (**1**) with Raney nickel-aluminum alloy under basic conditions. The reduction is dependent upon the nature of the substituent on the 2-position of **1**.

EXPERIMENTAL

Melting points were determined on a Yanaco micro melting point apparatus (MP 500D) and are uncorrected. ^{1}H NMR spectra were obtained on a JEOL JNM-LA (400 MHz). MS spectra were obtained on a JMS-01SA-2 mass spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed at Elemental Analytical Center, Kyushu University. Column chromatography was carried out on silica gel (Wako gel C-300). Sonication was carried out by using Kaijyo Denki 100a (100V, 0.8 A, 38 KHz, Kaijyo Denki Co. Ltd.). Raney nickel-aluminum alloy (Ni/Al = 50/50 (wt/wt)) was purchased from Kishida Chemical Co. Ltd.

Preparation of 2-substituted 9-aminoacridines.

9-Amino-2-bromoacridine (1b),[9] **9-amino-2-methylacridine (1d)**,[10] and **9-amino-2-methoxyacridine (1e)**[11] were prepared according to method reported previously. Compounds (**1c**, **1f**, and **1g**) were prepared as follows.

9-Amino-2,7-dibromoacridine (1c).[12,13] A mixture of 9-aminoacridine (1.94 g, 10 mmol) and benzyltrimethylammonium tribromide (7.80 g, 20 mmol) in acetic acid (40 mL) was heated at 70°C. Then, $ZnCl_2$ (2.00 g) was added to the mixture and it was heated at the temperature for 3 h. Precipitates were filtered and recrystallized from ethanol, giving **1c-H_2O-0.5HBr** (1.58 g, 39%): mp >300°C; ^{1}H NMR (DMSO-d_6): 7.89 (2H, d, J = 8.8 Hz), 8.14 (2H, d, J = 8.8 Hz), 8.97 (2H, s), 10.17 (2H br s, D_2O-exchanged), 14.30 (0.5H br s, D_2O-exchanged); MS: *m/z* 354, 352, 350 (M^+). *Anal.* Calcd for

($C_{13}H_8N_2Br_2$+ H_2O + 0.5HBr): C, 38.04; H, 2.58; N, 6.82. Found: C, 38.35; H, 2.47; N, 6.90.

Preparation of 9-amino-2-phenylacridine (1f). This compound was prepared from 2-bromo-9-chloroacridine (**5**)[14] *via* a sequence of reactions of Suzuki-Miyaura coupling[15, 16] of **5**, phenoxylation of 2-phenyl-9-chloroacridine (**6**), and amination of 2-phenyl-9-phenoxyacridine (**7**), as is described below.

Suzuki-Miyaura coupling of 5. A mixture of **5** (3.20 g, 11 mmol), phenylboronic acid (1.34 g, 11 mmol), aqueous sodium carbonate (2M, 12 mL, 24 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.2mg, 0.023 mol %) in dimethoxyethane (90 mL) was stirred at 80°C for 4 h under argon. The reaction mixture was poured into water (20 mL), extracted with chloroform (50 mL x 2). The organic layer was washed with water (30 mL x 2), dried over magnesium sulfate, and evaporated *in vacuo*, to leave the residue, which was chromatographed by using a 9:1-mixture of hexane/chloroform to give **6** (2.51 g, 79%): mp 137-138°C, pale yellow needles (hexane/chloroform = 2/1); ^{1}H NMR ($CHCl_3$): 7.45 (1H, t, *J* = 7.6 Hz), 7.55 (2H, t, *J* = 7.6 Hz), 7.62-7.66 (1H, m), 7.78-7.84 (3H, m), 8.10 (1H, dd, *J* = 4.4 and 2.0 Hz), 8.23 (1H, t, *J* = 4.4 Hz), 8.29 (1H, t, *J* = 4.4 Hz), 8.43 (1H, dd, *J* = 4.4 and 0.8 Hz), 8.59 (1H, d, *J* = 0.8 Hz); MS: *m/z* 291, 289 (M^+). *Anal*. Calcd for $C_{19}H_{12}NCl$: C, 78.76; H, 4.17; N, 4.83. Found: C, 78.56; H, 4.16; N, 4.82.

9-Phenoxy-2-phenylacridine (**7**). A mixture of **6** (2.00 g, 6.90 mmol) in phenol (10 mL) was stirred at 70°C for 4 min. The reaction mixture was poured into aqueous sodium hydroxide (6N, 100 mL), extracted with chloroform (30 mL x 2), and the extract was washed with water (50 mL x 2), dried over magnesium sulfate, and evaporated *in vacuo*, to give a mixture of **6** and **7**. Column chromatography of the mixture by using a 9:1-mixture of hexane/chloroform gave **7-0.5H_2O** (1.76 g, 72%): mp 182-183°C, yellow plates (hexane/chloroform = 5/1); ^{1}H NMR (DMSO-d_6): 6.96 (2H, dd, *J* = 8.8 and 1.2 Hz), 7.10 (1H, t, *J* = 7.2 Hz), 7.34 (2H, t, *J* = 7.2 Hz), 7.42 (1H, t, *J* = 7.2 Hz), 7.50 (2H, t, *J* = 7.2 Hz), 7.61 (1H, t, *J* = 7.2 Hz), 7.72 (2H, d, *J* = 7.2 Hz), 7.86-7.93 (1H, m), 8.06 (1H, d, *J* = 8.0 Hz), 819-8.28 (3H, m), 8.34 (1H, dd, *J* = 9.2 and 0.8 Hz); MS: *m/z* 347 (M^+). *Anal*. Calcd for $C_{25}H_{17}NO$ + 0.5H_2O: C, 84.25; H, 5.09; N, 3.93. Found: C, 84.17; H, 4.89; N, 3.90.

Amination of 7. Compound (**7**) was subjected to amination according to the method reported previously,[17] giving the desired **9-amino-2-phenylacridine (1f)** (73%): mp 215-216°C (lit.,[7] 215-216°C); ^{1}H NMR (DMSO-d_6): 7.33 (2H, t, *J* = 7.6 Hz), 7.38 (2H, t, *J* = 7.6 Hz), 7.52 (1H, t, *J* = 7.6 Hz), 7.65 (1H, t, *J* = 7.6 Hz), 7.83 (1H, d, *J* = 8.8 Hz), 7.91 (3H, t, *J* = 9.2 Hz), 8.24 (1H, dd, *J* = 8.0 and 2.0 Hz), 8.40 (1H, d, *J* = 8.8 Hz), 8.71 (1H, d, *J* = 2.0 Hz); MS: *m/z* 270 (M^+).

Reduction of 2-substituted 9-aminoacridines with nickel-aluminum alloy. Typical Procedure. To a stirred mixture of **1a** (388 mg, 2 mmol), aqueous sodium hydroxide (10%, 50 mL) and dioxane (15 mL), nickel-aluminum alloy (266 mg for every 2 min, total amount of 4.00 g) was added in portions at 95-97°C (bath temperature) within 30 min under sonication. After the addition was completed, the reaction mixture was stirred at 95-97°C (bath temperature) for 3 h, and then cooled to rt. The insoluble materials were

filtered over celite and washed with ethyl acetate (20 mL). The filtrate and the washings were combined and the organic layer was separated, washed with sat. aqueous sodium chloride (80 mL x 2), dried over magnesium sulfate, and evaporated *in vacuo*. The residue was subjected to column chromatography, and compound **4** (40 mg, 11%), **2a** (313 mg, 79%) and **3a** (trace amount) were obtained, each from the fractions eluted with chloroform, a 95:5-mixture of chloroform and ethanol, and ethanol.

9-Amino-1,2,3,4-tetrahydroacridine (2a): mp 179-181°C (lit.,[18] 181-183°C).

9-Amino-7-methyl-1,2,3,4-tetrahydroacridine (2d): mp 228-230°C (lit.,[18] 231-233°C).

9-Amino-7-methoxy-1,2,3,4-tetrahydroacridine (2e): mp 206-208°C (lit.,[18] 210-214°C).

9-Amino-1,2,3,4,5,6,7,8-octahydroacridine (3a): mp 210-211°C (lit.,[19] 218-219°C).

9-Amino-2-phenyl-1,2,3,4,5,6,7,8-octahydroacridine (3f). Compound (**3f**) was obtained from column chromatography using a 95:5-mixture of ethyl acetate and ethanol as an eluant. Recrystallization from a 9:1-mixture of hexane and chroroform gave **3f** as colorless plates, mp 169-170°C; ^{1}H NMR ($CDCl_3$): 1.78-2.31 (6H, m), 2.37-2.51 (3H, m), 2.68-2.89 (3H, m), 2.92-3.09 (3H, m), 3.95-4.09 (2H, br s, D_2O-exchanged), 7.19-7.42 (5H, m). HRMS calcd for $C_{19}H_{22}N_2$: 278.1783. Found: 287.1783 (M^+).

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