REDUCTION OF 9-SUBSTITUTED ACRIDINES WITH NICKEL-ALUMINUM ALLOY

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Abstract- 9-Methyl-, 9-ethyl-, 9-propyl-, 9-isopropyl-, and 9-phenylacridines were treated with nickel-aluminum alloy in hydrochloric acid to give the corresponding 1,2,3,4,5,6,7,8-octahydroacridines and 9,10-dihydroacridines. The yields are dependent upon the C-9 substituent.

INTRODUCTION

Catalytic hydrogenation of polynuclear heterocycles such as acridine, which is one of the infamous mutagenic environmental pollutants, [1] has been investigated, especially in the field of coal up-grading and liquefaction.[2] Partially reduced acridines are interesting because of their biological activity,[3] also in regard to studies of the mutagenicity[4] of acridine itself. Thus, today there is still a demand for new and cheap reductants of this class of molecules.[5]

One such reductant may well be Raney aluminum alloy, as it is known that treatment of organic substrates with Raney aluminum alloy in either aqueous alkaline or acidic solution presents a convenient and practical reductive method for various types of compounds.[6,7] Thus, halophenols could be hydrogenated easily to the corresponding cyclohexanols under mild conditions.[7] It has been found that the reduction with Raney aluminum alloy can be accelerated by ultrasonic irradiation in many cases.[7a] Previously, it had also been noted that in the reduction of quinoline, 5-methylquinoline and isoquinoline with nickel-aluminum alloy under basic conditions, only the pyridine-ring of the substrates is reduced, giving the corresponding 1,2,3,4-tetrahydro derivatives.[8] Here, we report that the reduction of 9-alkyl substituted acridines with Raney nickel alloy can afford 9-alkyl-9,10-dihydroacridines and/or 9-alkyl-1,2,3,4,5,6,7,8-octahydroacridines.

RESULTS AND DISCUSSION

The reduction of 9-methylacridine (**1a**) with Raney aluminum alloy was carried out in both alkaline and

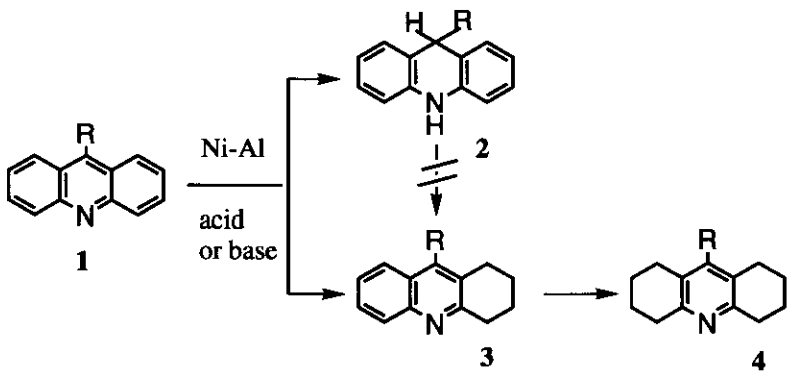
acidic media and the results are summarized in Tables 1-2 and Scheme 1. As expected, nickel-aluminum alloy is more reactive in the reduction of acridine than either copper- or cobalt-aluminum alloy (Table 1).[9] The reduction of 9-methylacridine (**1a**) gives a mixture of 9-methyl-9,10-dihydroacridine (**2a**), in which the pyridine-ring has been reduced, and of benzo-ring reduced derivatives **3a** and **4a**. Sonication during the reductions was effective. Similar treatment of acridine itself only gave 9,10-dihydroacridine. Further hydrogenation of 9,10-dihydroacridine (**2a**) proved to be unsuccessful under the same conditions.

Table 1. Effect of the alloy on reduction of 9-methylacridine (**1a**) in 10% sodium hydroxide solution.[a)]

Substrate (mmol)	Alloy (g)	Sonication	Product ; Yield %[b)]
1a (50)	Ni-Al (7.5)	+	**2a**; 41 (47), **3a**; 36 (45), **4a**; 1 (8)
1a (50)	Ni-Al (7.5)	–	**2a**; 55 (55), **3a**; 28 (39), **4a**; 0 (5)
1a (50)	Cu-Al (7.5)	–	**1a**; (7), **2a**; (93)
1a (50)	Co-Al (7.5)	–	**1a**; (42), **2a**; (52), **3b**; (6)

a) Reaction bath temp: 95 °C; reaction time: 3 h.

b) Relative ratios determined by ^{1}H NMR spectra are given in parentheses.



a; R = Me, **b**; R = Et, **c**; R = Pr, **d**; R = *iso*-Pr, **e**; R = Ph

Scheme 1

The reduction of **1a** with nickel-aluminum alloy was carried out by using procedures (A)-(C). In (A)-(C), sonication was applied, where procedures (A)-(C) are as follows: (A) the alloy was added in portions to a mixture of **1** and 10% aq. sodium hydroxide solution, (B) the alloy was added in portions to a mixture of **1** and 10% hydrochloric acid, and (C) a solution of **1** in a mixed solvent of 10% hydrochloric acid and dioxane was added dropwise to a mixture of the alloy and dioxane.

For the preparation of tetrahydroacridine (**3a**), formation of (**4a**) needs to be suppressed as the separation of **3a** and **4a** by column chromatography is somewhat troublesome. At the best, **3a** was obtained in 36% isolated yield when the reduction of **1a** was carried out by using procedure (A) (Entry 1, Table 2). Reduction by procedure (A) becomes less effective with increasing size of the substituent. Thus, 9-isopropylacridine (**1d**) gave 9,10-dihydroacridine (**2d**) as the sole reduction product, together with

unchanged **1d**. The ratio of **1d/2d** is 1/1. Similarly, 9-phenylacridine (**1e**) gave a 7/3-mixture of **1e/2e**. The results given in Table 2 show that **1a** is reduced more readily to the tetra- and octahydro compounds (**3a**) and (**4a**) in acidic media than in alkaline media. The easy-to-operate procedure (C) is suitable for the preparation of **4a**. **4a** is produced in 80% isolated yield (see Table 3).

Table 2. Reduction of 9-substituted acridines (**1**) employing different experimental procedures.[a)]

Entry	Substrate[b)]	Procedure	Ni/Al (g)	Product (Rel. Yield, %)[c)]
1	**1a**	A	7.5	**2a** (47), **3a** (45), **4a** (8)
2	**1b**	A	7.5	**2b** (56), **3b** (35), **4b** (9)
3	**1c**	A	7.5	**2c** (70), **3c** (30)
4	**1d**	A	7.5	**1d** (51), **2d** (49)
5	**1e**	A	7.5	**1e** (70), **2e** (30)
6	**1a**	B	7.5	**2a** (10), **3a** (30), **4a** (40)
7	**1a**	B	10.0	**2a** (2), **3a** (10), **4a** (88)
8	**1a**	C	7.5	**2a** (1), **3a** (11), **4a** (88)
9	**1a**	C	10.0	**2a** (1), **3a** (5), **4a** (94)

a) The reaction mixture was sonicated at 95 °C (bath temperature) for 3h.

b) Fifty mmols of the substrate (**1**) was used. c) Relative ratios determined by ^{1}H NMR spectra.

A number of other 9-alkyl-substituted acridines (**1b-1e**) were reduced using procedure (C) (Table 3). Formation of dihydroacridines (**2**) competes with the benzo-ring reduction in the cases of **1b**, **1c**, and **1d**, which possess longer and bulkier alkyl chains. Under the same reaction conditions, 9-phenylacridine (**1e**) was reduced less readily, giving a mixture of di-, tetra- and octahydroacridines (**2e**, **3e**, and **4e**).

Table 3. Reduction of 9-substituted acridines (**1**) in 10% hydrochloric acid.[a)]

Substrate (mmol)	R	Product, Isolated Yield (%)[b)]
1a (50)	CH_3	**2a** -[c)] (1), **3a** 1 (5), **4a** 80 (94)
1b (50)	C_2H_5	**2b** 65 (73), **3b** -[c)] (1), **4b** 19 (26)
1c (50)	C_3H_7	**2c** 50 (59), **3c** -[c)] (3), **4c** 32 (38)
1d (50)	*iso*-C_3H_7	**2d** 43 (55), **3d** -[c)] (7), **4d** 33 (38)
1e (50)	Ph	**2e** 14 (22), **3e** 14 (17), **4e** 58 (66)

a) Procedure (C) was employed with using 10.0 g of Ni-Al alloy.

b) Relative ratios determined by ^{1}H NMR are given in parentheses.

c) (-) denotes that the yield is less than 1%.

In the reduction of **1**, hydrogenation of the benzo ring leading to **3** competes with the reduction of the pyridine ring to give **2** (Scheme 1). Dihydroacridine (**2**) is inert under the conditions used. This was confirmed by the fact that under the conditions of procedure (C), **3a** gave **4a**, but **2a** was recovered

unchanged. Although the mechansim of this heterogenic reaction is not yet known in full detail, it is suggested that both electronic and steric effects of the substituents play a role. While an increase of electron density in the central ring and thus of the basicity of the acridine favors a reduction of the annelated benzo rings leading to the tetrahydro- and octahydroacridines, an increase in steric demand of the substituent disfavors this reaction. **1e** is a special case; here the possible conjugation of the phenyl group with the core pyridine unit overrides any steric effects.[10]

Although the yields are dependent upon the substituent, the treatment of 9-alkylacridines **1** with nickel-aluminum alloy in acidic solution provides a convenient method for preparing 9-substituted 1,2,3,4,5,6,7,8-octahydroacridines (**4**). These may also be of interest as potent basic structures in medicinal chemistry[3] as are the 1,2,3,4-tetrahydroacridines.[11]

EXPERIMENTAL

Melting points were determined on a Yanaco micromelting point apparatus (MP 500D) and are uncorrected. ^{1}H NMR spectra were obtained on a JEOL JNM-LA 300 in a $CDCl_3$ solution. MS spectra were obtained at 75 eV by using a JMS-01SA-2 mass spectrometer. Elemental analyses were performed at Elemental Analytical Center, Kyushu University. Columm chromatography was carried out on silica gel (Wako gel C-300).

Typical Procedures.

Procedure (A) : To a stirred mixture of **1a** (0.965 g, 5 mmol), aq. sodium hydroxide (10%, 50 mL) and dioxane (15 mL), nickel-aluminum alloy (0.5 g for every 2 min) was added in portions at 90 °C (bath temperature) within 30 min. After the addition was completed, the reaction mixture was stirred at 95 °C (bath temperature) under sonication for 3 h and then cooled to rt. The insoluble materials were filtered over celite and washed with ethyl acetate (50 mL). The filtrate and washings were combined and extracted with ethyl acetate (100 mL). The extract was washed with sat. aq. sodium chloride, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was subjected to column chromatography on silica gel (eluant: chloroform) to afford **2a** (400 mg, 41%), **3a** (354 mg, 36%), and **4a** (9 mg, 1%) in that order.

Procedure (B) : To a stirred mixture of **1a** (0.965 g, 5 mmol), hydrochloric acid (10%, 50 mL) and dioxane (8 mL), nickel-aluminum alloy (0.5 g for every 2 min) was added in portions at 95 °C (bath temperature) within 30 min under sonication. After the addition was completed, the reaction mixture was stirred at 95 °C (bath temperature) under sonication for 3 h and then cooled to rt. The insoluble materials were filtered over celite and washed with ethyl acetate (50 mL). The filtrate and washings were combined and extracted with ethyl acetate (100 mL). The extract was washed with sat. aq. sodium chloride, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was analyzed by ^{1}H NMR spectroscopy to contain **2a**, **3a**, and **4a** (10 : 30 : 60).

Procedure (C) : To a stirred mixture of nickel-aluminum alloy (10.0 g) and dioxane (7 mL), a mixture

of **1a** (0.965 g, 5 mmol), hydrochloric acid (10%, 50 mL) and dioxane (8 mL) was added dropwise at 95 °C (bath temperature) within 60 min and under sonication. After the addition was completed, the reaction mixture was stirred at 95 °C (bath temperature) under sonication for 3 h and then cooled to rt. The insoluble materials were filtered over Celite and washed with ethyl acetate (50 mL), dilute aq. sodium hydroxide (0.5%, 100 mL), and once again ethyl acetate (50 mL). The filtrate and washings were combined, made alkaline with aqueous sodium hydroxide (20%) and extracted with ethyl acetate (100 mL). The extract was washed with sat. aq. sodium chloride, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was column chromatographed on silica gel (eluant: chloroform) to give **3a** (9 mg, 1%) and **4a** (802 mg, 80%).

Compounds (**1a**,[12-14] **1b**,[12,14] **1c**,[14] **1d**,[12] **1e**,[15] **2a**,[12,16,17] **2b**,[12,18,19] **2c**,[17] **2d**,[12] **2e**,[15] **3a**,[20,21] **3c**,[21] **4a**,[22] **4b**,[22] and **4e**[22] have been reported previously. Physical and spectral properties of newly prepared **3b**, **3e**, **4c**, and **4d**) are given below.

9-Ethyl-1,2,3,4-tetrahydroacridine (3b); white solid, mp 47-49 °C (Kugelrohr, 175 °C/1.8 Torr) ; ^{1}H NMR ($CDCl_3$): 1.25 (3H, t, J 7.6 H), 1.85-2.02 (4H, m), 2.85-2.98 (2H, m), 3.04 (2H, q, J 7.6 Hz), 3.08-3.19 (2H, m), 7.40-7.50 (1H, m), 7.53-7.63 (1H, m), 7.90-8.00 (2H, m); HRMS calcd for $C_{15}H_{17}N$: 211.1361. Found: 211.1361. *Anal.* Calcd for ($C_{15}H_{17}N$ + 0.4 H_2O); C, 82.45; H, 8.21; N, 6.41. Found; C, 82.58; H, 8.24; N, 6.35.

9-Phenyl-1,2,3,4-tetrahydroacridine (3e); Colorless prisms, mp 138-139 °C (petr. benzine); ^{1}H NMR ($CDCl_3$): 1.73-1.85 (2H, m), 1.89-1.21 (2H, m), 2.51-2.64 (2H, m), 3.11-3.24 (2H, m), 7.30-7.64 (7H, m), 7.98-8.05 (2H, m); HRMS calcd for $C_{19}H_{17}N$: 259.1361. Found: 259.1357. *Anal.* Calcd for $C_{19}H_{17}N$; C, 87.99; H, 6.61; N, 5.40. Found; C, 87.76; H, 6.59; N, 5.33.

9-Propyl-1,2,3,4,5,6,7,8-octahydroacridine (4c); pale yellow oil (Kugelrohr, 175 °C/1.2 Torr); ^{1}H NMR ($CDCl_3$): 1.02 (3H, t, J 7.4 Hz), 1.35-1.51 (2H, m), 1.71-1.89 (8H, m), 2.40 (2H, m), 2.60-2.78 (4H, m), 2.80-2.95 (4H, m); MS: m/z 229 (M^+). *Anal.* Calcd for $C_{16}H_{23}N$; C, 83.78; H, 10.11; N, 6.11. Found; C, 83.36; H, 10.12; N, 6.03.

9-Isopropyl-1,2,3,4,5,6,7,8-octahydroacridine (4d); white solid, mp 73-74 °C (Kugelrohr, 190 °C/2.1 Torr) ; ^{1}H NMR ($CDCl_3$): 1.33 (6H, d, J 7.6 Hz), 1.70-1.90 (8H, m), 2.68-2.93 (8H, m), 3.40 (1H, sept, J 7.3 Hz); MS: m/z 229 (M^+). *Anal.* Calcd for $C_{16}H_{23}N$; C, 83.78; H, 10.11; N, 6.11. Found; C, 83.70; H, 10.09; N, 6.08.

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