Synthesis of 4-Aminocycloheptimidazoles

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2-Methyl- **1a**, 2-phenyl- **1b**, and 2-amino-4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole (**1c**) were treated with hydrazoic acid to give the corresponding 4-aminocycloheptimidazoles, respectively. However, the reaction of 4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole gave complex material. Some approaches to the synthesis of 4-aminonocycloheptimidazole itself are also described.

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For cycloheptimidazole (1,3-diazaazulene) bearing an amino group, four isomers are possible (Figure 1). Of them, 2- **A** [2], 5- **C** [3], and 6-amino-substituted isomer **D** [4] have been previously reported, while 4-aminocycloheptimidazole **B** and its derivatives have not been prepared. These 4-amino-substituted isomers have reactive amino group adjacent to the imidazole nitrogen atom in the seven-membered ring. Thus, the present work was carried out on purpose to synthesize 4-aminocycloheptimidazoles which are considered to be useful and important precursors to new types of nitrogen-containing tricycle-fused ring systems.

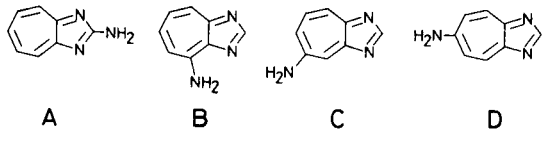


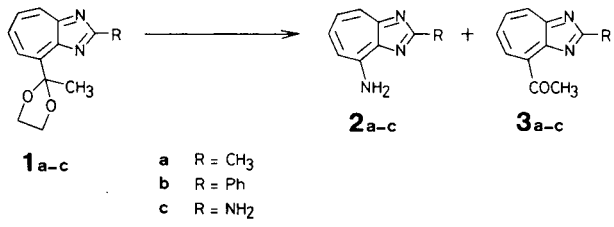
Figure 1

Results and Discussion.

Some cycloheptimidazoles bearing an amino group in the seven-membered ring have been obtained by application of the Schmidt reaction to 5- and 6-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazoles [3,4].

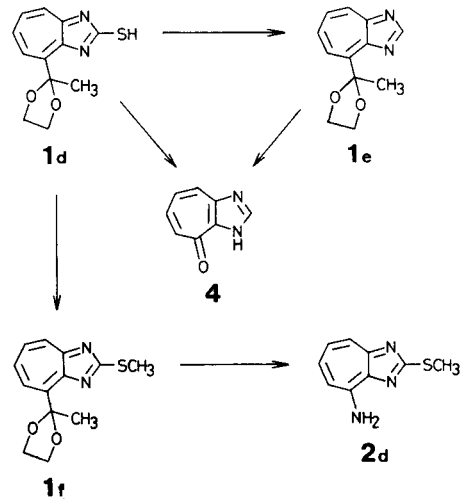
A mixture of 2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole (**1a**) [5] and sodium azide in concentrated sulfuric acid was stirred for 2 hours at room temperature to afford 4-amino-2-methylcycloheptimidazole (**2a**) in 34% yield. This compound is less stable than the other 4-aminocycloheptimidazoles bearing an amino or a phenyl group in the 2-position. The reaction of 4-(2-methyl-1,3-dioxolan-2-yl)-2-phenylcycloheptimidazole (**1b**) [5] with hydrazoic acid gave 4-amino-2-phenylcycloheptimidazole (**2b**) and 4-acetyl-2-phenylcycloheptimidazole (**3b**) [6] in 84 and 15% yields, respectively. The former is the product by the Schmidt reaction, while the latter is a hydrolysis product. 2-Amino-4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole (**1c**) [5] was also treated with hydrazoic acid to give 2,4-diaminocycloheptimidazole (**2c**) [7] and 4-acetyl-2-aminocycloheptimidazole (**3c**) [6] in 58 and 9% yields, respectively.

Scheme 1



In an approach to the synthesis of 4-aminocycloheptimidazole having no substitutent at the 2-position, 4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole, which is a precursor, has not been obtained in the reaction of 2-(2-methyl-1,3-dioxolan-2-yl)-7-methoxytropone with formamidine [5]. Thus, we attempted the desulfurization of 2-mercapto-4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole (**1d**). Compound **1d** was stirred in 12% hydrogen peroxide solution at room temperature to give 4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole (**1e**) as yellow prisms in 27% yield. This reaction was carried out at elevated temperature to afford 1,8-dihydrocycloheptimidazol-8-one (**4**) as pale yellow plates in 50% yield. The compound **1e** was also heated with hydrogen peroxide to convert to **4** in 55% yield. It is considered that the formation of the 1,8-dihy-

Scheme 2



drocycloheptimidazol-8-one **4** was initiated by attack of hydrogen peroxide to the carbon atom at the 4-position. The reaction of the cycloheptimidazole **1e** with hydrazoic acid gave complex tarry material. 2-Mercapto-4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole (**1d**) was also treated with hydrazoic acid to give a complex mixture. Then, the 2-mercapto-substituted compound **1d** was treated with methyl iodide in the presence of sodium ethoxide to afford 4-(2-methyl-1,3-dioxolan-2-yl)-2-methylthiocycloheptimidazole (**1f**) in 71% yield. The treatment of compound **1f** with hydrazoic acid gave 4-amino-2-methylthiocycloheptimidazole (**2d**) in 63% yield. However, an approach to the reductive removal of the methylthio group of **2** failed.

The chemical reactions of 4-aminocycloheptimidazoles will be published near furture.

EXPERIMENTAL

Measurements.

The melting points were determined with a Yanagimoto MP-S2 apparatus and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrophotometer, and the uv spectra on a Hitachi EPS-3T and a Hitachi 200-20 spectrophotometer. The ^{1}H nmr spectra were recorded with a JEOL JNM-PMX60SI spectrometer (60 MHz). The mass spectra were obtained with a JEOL JMS-01-SG2 spectrometer.

Reaction of 4-(2-Methyl-1,3-dioxolan-2-yl)cycloheptimidazoles **1a-c** with Hydrazoic Acid.

To a stirred solution of the cycloheptimidazoles **1a-c** (1.0 mmole) in concentrated sulfuric acid (2 ml) was added sodium azide (98 mg, 1.5 mmoles) little by little. After stirring for 2 hours, the reaction mixture was neutralized with 2*M* sodium hydroxide solution and extracted with chloroform. The evaporated residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with ethyl acetate to give 4-aminocycloheptimidazoles **2a-c** and 4-acetylcycloheptimidazoles **3b,c**.

4-Amino-2-methylcycloheptimidazole (**2a**).

This compound was obtained as yellow prisms (from ethanol-cyclohexane) in a yield of 54 mg (34%), mp 235° dec; ir (potassium bromide): ν max 3300 cm^{-1} (NH); uv (methanol): λ max 247 (log ϵ 4.46), 318 (3.94), 400 nm (3.75); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.61 (3H, s, CH_3), 7.0-8.5 (3H, m, H-5,6,7), 7.9-8.5 (3H, m, H-8, NH_2). Found: m/z 159.0796 (M^+). Calcd. for $C_9H_9N_3$: M, 159.0797.

4-Amino-2-phenylcycloheptimidazole (**2b**).

This compound was obtained as yellow prisms (from ethanol-cyclohexane) in a yield of 190 mg (84%), mp 277-278°; ir (potassium bromide): ν max 3300 cm^{-1} (NH); uv (methanol): λ max 265 (log ϵ 4.84), 342 (4.24), 423 nm (4.32); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 6.9-7.8 (7H, m), 7.8-8.8 (4H, m).

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.70; H, 5.27; N, 19.00.

4-Acetyl-2-phenylcycloheptimidazole (**3b**).

This compound was obtained in a yield of 37 mg (15%), mp 142-143° (lit [6], 142-143°).

2,4-Diaminocycloheptimidazole (**2c**).

This compound was obtained as yellow prisms (from chloroform-hexane) in a yield of 95 mg (58%), mp 199-201° (lit [7], 208-209.5°); ir (potassium bromide): ν max 3450 (NH), 3300 cm^{-1} (NH); uv (methanol): λ max 271 (log ϵ 4.34), 345 (3.95), 423 nm (4.02); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 6.40 (2H, br, NH_2), 6.93 (2H, br, NH_2), 7.1-7.5 (3H, m, H-5,6,7), 7.6-8.0 (1H, m, H-8).

Anal. Calcd. for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.85; H, 5.11; N, 35.19.

4-Acetyl-2-aminocycloheptimidazole (**3c**).

This compound was obtained in a yield 17 mg (9%), mp 213-214° (lit [6], 213-215°).

Treatment of 2-Mercapto-4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole (**1d**) with Hydrogen Peroxide.

a) To a stirred suspension of **1d** (260 mg, 1.0 mmole) in water (5 ml) was added 30% hydrogen peroxide (7 ml) at room temperature. After stirring for 15 minutes, the crystals were dissolved. The ice-cooled solution was neutralized with a saturated sodium hydrogencarbonate solution and extracted with chloroform. The evaporated residue was twice chromatographed on a Wakogel B-10 plate (30 x 30 cm) with ethyl acetate. The yellow fraction was recrystallized from benzene-hexane to afford 4-(2-methyl-1,3-dioxolan-2-yl)cycloheptimidazole (**1e**) as yellow prisms, yield 162 mg (72%), mp 126-127°; uv (methanol): λ max 227 (log ϵ 4.42), 258 (4.56), 303 (3.80), 390 nm (3.06); ^{1}H nmr (deuteriochloroform): δ 2.16 (3H, s, CH_3), 3.7-4.5 (4H, m, OCH_2CH_2O), 8.0-9.1 (4H, m, H-5,6,7,8), 9.14 (1H, s, H-2). Found: m/z 216.0903 (M^+). Calcd. for $C_{12}H_{12}N_2O_2$: M, 216.0899.

b) A suspension of **1d** (253 mg, 1.0 mmole) in a mixture of 30% hydrogen peroxide (2 ml) and water (5 ml) was heated on a water bath for 5 minutes. The reaction mixture was worked up, as mentioned above. The evaporated residue from the extract was recrystallized from benzene-hexane to afford 1,8-dihydrocycloheptimidazol-8-one (**4**) as pale yellow plates, yield 75 mg (50%), mp 167-168°; ir (chloroform): ν max 3350 (NH), 1620 cm^{-1} (C=O); uv (methanol): λ max 290 sh (log ϵ 3.72), 303 (3.82), 352 sh (3.69), 369 nm (3.64); ^{1}H nmr (deuteriochloroform): δ 6.8-7.8 (4H, m, H-5,6,7, NH), 7.8-8.1 (1H, m, H-4), 8.26 (1H, s, H-2); ms: m/z (%) 146 (M^+; 100), 118 (M-CO; 78). Found: m/z 146.0461 (M^+). Calcd. for $C_8H_6N_2O$: M, 146.0480.

Conversion of the Cycloheptimidazole **1e** to Compound **4**.

A suspension of **1e** (162 mg, 0.8 mmole) in a mixture of 30% hydrogen peroxide (2 ml) and water (5 ml) was heated on a water bath for 5 minutes. The mixture was worked up, as mentioned above, and chromatographed on a Wakogel B-10 plate (30 x 30 cm) with ethyl acetate to give 1,8-dihydrocycloheptimidazol-8-one (**4**) (60 mg, 55%).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.77; H, 4.31; N, 18.93.

Methylation of the 2-Mercaptocycloheptimidazole (**1d**).

To a solution of **1d** (496 mg, 2.0 mmoles) in sodium ethoxide medium prepared from sodium (50 mg, 2.2 mmoles) and absolute ethanol (20 ml), was added methyl iodide (330 mg, 2.3 mmoles). The mixture was refluxed for 30 minutes. After removal of the solvent, the residue was triturated with water and extracted with chloroform. The evaporated residue from the extract was recrystallized from benzene-cyclohexane to give 4-(2-methyl-1,3-dioxo-

lan-2-yl)-2-methylthiocycloheptimidazole (**1f**) as reddish orange prisms: yield 374 mg (71%), mp 154-155°; ^{1}H nmr (deuteriochloroform): δ 2.13 (3H, s, C-CH_3), 2.85 (3H, s, SCH_3), 3.7-4.4 (4H, m, OCH_2CH_2O), 7.7-8.1 (2H, m, H-6,7), 8.2-8.7 (2H, m, H-5,8).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.23; H, 5.63; N, 10.41.

Reaction of 4-(2-Methyl-1,3-dioxolan-2-yl)-2-methylthiocycloheptimidazole (**1f**) with Hydrazoic Acid.

To a solution of **1f** (266 mg, 1.0 mmole) in concentrated sulfuric acid (2 ml) was added sodium azide (159 mg, 2.4 mmoles) little by little. After stirring for 2 hours at room temperature, the mixture was diluted with water, neutralized with 2*M* sodium hydroxide solution, and extracted with chloroform. The evaporation residue (199 mg) from the extract was recrystallized from ethyl acetate-hexane to give 4-amino-2-methylthiocycloheptimidazole (**2d**) as yellow prisms, yield 122 mg (63%), mp 180-182° dec; ir (potassium bromide): ν max 3280 cm^{-1} (NH); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.70 (3H, s, CH_3), 7.0-7.7 (3H, m, H-5,6,7), 7.7-8.6 (3H, m, H-8, NH_2).

Anal. Calcd. for $C_9H_8N_3S$: C, 56.52; H, 4.74; N, 21.97. Found: C, 56.31; H, 4.78; N, 22.08.

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