

Preparation of *N*-Aryl-2,4-diaminopentanes
by the Ring Opening Reaction of
1-Aryl-3,4,5,6-tetrahydro-2-(1*H*)pyrimidinones

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1-Aryl-3,4,5,6-tetrahydro-2-(1*H*)pyrimidinones (I) underwent reductive ring opening reaction with lithium aluminum hydride to afford *N*-aryl-2,4-diaminopentanes (II) in good yields. On the other hand, 3,4,5,6-tetrahydro-3,4,6-trimethyl-1-phenyl-2-(1*H*)pyrimidinone (V) gave only cyclic diamine, 3,4,6-trimethyl-1-phenylhexahydropyrimidine (VI), in 60% yield.

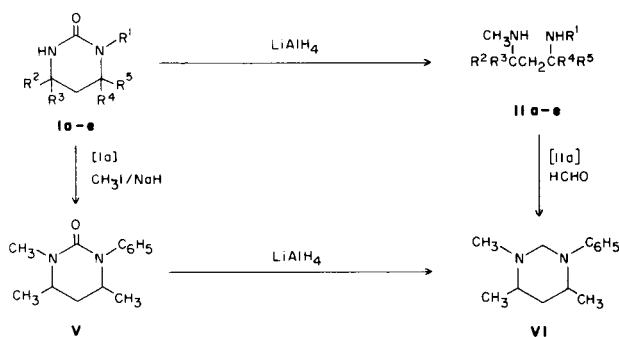
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Diamines are useful compounds as synthetic intermediates and ligands of metal chelates (1). Although many papers have been reported on the synthesis of 2,4-diaminopentanes (2), the great majority of these works has been concerned with *N*-unsubstituted or *N*-alkyl-substituted-2,4-diaminopentanes. Hutchins and Maryanoff reported on the preparation of 2,4-diaminopentane from 3,4,5,6-tetrahydro-2-(1*H*)pyrimidinone by the hydrolysis with 60% sulfuric acid under heating at 160° for 4 days (3). In 1964 Larizza *et al.*, reported that *N,N,N'*-trisubstituted ureas were reduced with lithium aluminum hydride to give a mixture of two amines under drastic reaction conditions (4).

In the previous paper, we reported that 1-aryl-3,4,5,6-tetrahydro-4,6-dimethyl-2-(1*H*)pyrimidinones (I) were easily obtained in high yields by the reaction of 1-aryl-4,6-dimethyl-2-(1*H*)pyrimidinones with sodium borohydride in acetic acid (5). Since compounds I are regarded as *N,N,N'*-trisubstituted cyclic ureas, they seem to be important precursor for the preparation of *N*-aryl-2,4-diaminopentanes.

In this paper, we wish to describe on the preparation of *N*-aryl-2,4-diaminopentanes by reductive ring opening reaction of 1-aryl-3,4,5,6-tetrahydro-2-(1*H*)pyrimidinones.

When 3,4,5,6-tetrahydro-4,6-dimethyl-1-phenyl-2-(1*H*)pyrimidinone (Ia) was refluxed for 20 hours with lithium aluminum hydride in tetrahydrofuran/benzene mixture, colorless viscous oil, bp 58°/10⁻⁴ mm Hg, was obtained. The product had the formula C₁₂H₂₀N₂ and was found to be fairly basic. The ir absorption band at 1660 cm⁻¹ due to C=O stretching in Ia disappeared and the band at 3280 cm⁻¹ attributable to N-H stretching was observed. The nmr spectrum showed signals at δ 1.05 (d, 3H, J = 6.0 Hz, CH₃), 1.15 (d, 3H, J = 6.0 Hz, CH₃), and 2.34 (s, 3H, N-CH₃). Further, the nmr spectrum exhibited signals characteristic of an aniline moiety at δ 6.5-6.9 (m, 3H) and 7.1-7.4 (m, 2H), and observed two deuterium exchangeable protons at δ 2.94 (br s, 2H, 2N-H). From these data, two possible structures (IIa and III) were proposed. The methyl protons of dimethylamine appear at 2.43 ppm,



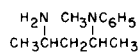
a: R¹ = C₆H₅, R² = R⁴ = H, R³ = R⁵ = CH₃

b: R¹ = 4-CH₃OC₆H₄, R² = R⁴ = H, R³ = R⁵ = CH₃

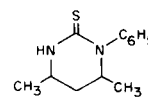
c: R¹ = 4-CH₃C₆H₄, R² = R⁴ = H, R³ = R⁵ = CH₃

d: R¹ = C₆H₅, R² = H, R³ = R⁴ = R⁵ = CH₃

e: R¹ = C₆H₅, R² = R³ = R⁴ = CH₃, R⁵ = H



III



IV

while those of *N,N*-dimethylaniline appear at 2.92 ppm (6). Further, compound IIa treated with formaldehyde to yield 3,4,6-trimethyl-1-phenylhexahydropyrimidine (VI). Thus the structure of III seemed to be unlikely, and the product was assigned to be 2-anilino-4-methylaminopentane (IIa). The reductive ring opening reaction of similar 3,4,5,6-tetrahydro-2-(1*H*)pyrimidinones with lithium aluminum hydride was examined and the results were summarized in Table 1 and Table 2. Also, the reduction of 3,4,5,6-tetrahydro-4,6-dimethyl-2-(1*H*)pyrimidinethione (IV) was carried out in the manner described above, but the starting material IV was recovered. Finally, we examined on the reduction of 3,4,5,6-tetrahydro-3,4,6-trimethyl-1-phenyl-2-(1*H*)pyrimidinone (V), which was regarded as tetrasubstituted urea, to give only compound VI which was formed by the reduction of carbonyl group.

It is concluded from these results that the preparation of *N*-aryl-2,4-diaminopentanes was accomplished by the

Table 1

Compound No	Bp °C/10 ⁻⁴ mmHg	Yield %	Formula	Analysis %		
				Calcd.	(Found)	
				C	H	N
IIa	58	75	C ₁₂ H ₂₀ N ₂	74.94 (74.67)	10.48 (10.49)	14.56 (14.27)
IIb	70	54	C ₁₃ H ₂₂ N ₂ O	70.22 (70.12)	9.97 (10.01)	12.60 (12.35)
IIc	60	59	C ₁₃ H ₂₂ N ₂ ·O·2H ₂ O	74.42 (74.46)	10.68 (10.76)	13.35 (13.41)
IId	42	37	C ₁₃ H ₂₂ N ₂	75.67 (75.55)	10.74 (10.81)	13.57 (13.67)
IIe	63	40	C ₁₃ H ₂₂ N ₂ ·O·1H ₂ O	75.07 (74.92)	10.68 (10.72)	13.47 (13.44)

Table 2

The IR and NMR Spectra of 2,4-Diaminopentanes (IIa-e)		
Compound No	IR Spectra (a)	NMR Chemical Shift (b)
	(N-H, cm ⁻¹)	δ (ppm)
IIa	3280	1.05 (d, 3H, J = 6.0 Hz), 1.15 (d, 3H, J = 6.0 Hz), 1.3-1.9 (m, 2H), 2.34 (s, 3H), 2.5-3.0 (m, 1H), 2.94 (br. s, 2H), 3.4-3.9 (m, 1H), 6.5-6.9 (m, 3H), and 7.1-7.4 (m, 2H)
IIb	3280	1.07 (d, 3H, J = 6.0 Hz), 1.17 (d, 3H, J = 6.0 Hz), 1.3-1.8 (m, 2H), 2.40 (s, 3H), 2.57 (br. s, 2H), 2.5-3.0 (m, 1H), 3.4-3.8 (m, 1H), 3.74 (s, 3H), and 6.5-6.9 (m, 4H)
IIc	3300	1.12 (d, 3H, J = 6.0 Hz), 1.15 (d, 3H, J = 6.0 Hz), 1.4-2.0 (m, 2H), 2.23 (s, 3H), 2.43 (s, 3H), 2.4-3.0 (m, 1H), 3.13 (br. s, 2H), 3.4-4.0 (m, 1H), 6.5-6.8 (m, 2H), and 6.9-7.2 (m, 2H)
IId	3280	1.05 (d, 3H, J = 6.0 Hz), 1.30 (s, 6H), 1.4-2.0 (m, 2H), 2.39 (s, 3H), 2.5-3.3 (m, 3H), 6.5-6.9 (m, 3H), and 7.0-7.3 (m, 2H)
IIe	3280	1.10 (s, 6H), 1.17 (d, 3H, J = 6.0 Hz), 1.4-2.0 (m, 2H), 2.34 (s, 3H), 3.2-4.0 (m, 3H), 6.5-6.9 (m, 3H), and 7.0-7.3 (m, 2H)

(a) Measured neat. (b) Measured in deuteriochloroform.

reductive ring opening reaction of 1-aryl-3,4,5,6-tetrahydro-2(1H)pyrimidinones on treatment with lithium aluminum hydride.

EXPERIMENTAL

All melting points and boiling points were uncorrected. IR spectra were obtained on a Jasco ITA-1 spectrophotometer. Nmr spectra were recorded on a Hitachi R-20 spectrometer using TMS as an internal standard.

Materials.

3,4,5,6-Tetrahydro-4,6,6-trimethyl-1-phenyl-2(1H)pyrimidinone (Id).

3,6-Dihydro-4,6,6-trimethyl-1-phenyl-2(1H)pyrimidinone (7) was reduced with sodium borohydride in acetic acid according to the method previously reported (5). Compound Id was recrystallized from benzene/hexane mixture and had mp 182-182.5°, 81% yield; ir: 3300, 1660, 1340, 1080, 760 and 700 cm⁻¹; nmr: δ 0.98 (s, 3H), 1.14 (d, 3H, J = 6.0 Hz), 1.30 (s, 3H), 1.5-1.8 (m, 2H), 3.4-3.9 (m, 1H), 5.66 (br s, 1H), and 7.0-7.5 (m, 5H).

Anal. Calcd. for C₁₃H₁₈N₂O: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.47; H, 8.33; N, 12.78.

3,4,5,6-Tetrahydro-4,4,6-trimethyl-1-phenyl-2(1H)pyrimidinone (Ie).

3,4-Dihydro-4,4,6-trimethyl-1-phenyl-2(1H)pyrimidinone (7) was worked up according to the manner described above. Compound Ie was recrystallized from ethyl acetate/hexane mixture and had mp 144-144.5°,

82% yield; ir: 3280, 1650, 1600, 1200, 1070, and 690 cm⁻¹; nmr: δ 0.96 (d, 3H, J = 6.0 Hz), 1.23 (s, 3H), 1.32 (s, 3H), 1.5-1.9 (m, 2H), 3.8-4.2 (m, 1H), 5.23 (br s, 1H), and 7.1-7.4 (m, 5H).

Anal. Calcd. for C₁₃H₁₈N₂O: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.74; H, 8.32; N, 12.92.

3,4,5,6-Tetrahydro-3,4,6-trimethyl-1-phenyl-2(1H)pyrimidinone (VI).

Compound Ia (4 mmoles) was stirred for 1 hour in dry tetrahydrofuran (20 ml) in the presence of sodium hydride (8mmoles), and then methyl iodide (16 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise to the mixture. After refluxing for another 1 hour, the reaction mixture was washed with water, then the organic layer was dried over anhydrous magnesium sulfate. The crude product VI was recrystallized from hexane and had mp 72-72.5°, 84% yield; ir: 1640, 1590, 1220, 760, and 690 cm⁻¹; nmr: δ 0.97 (d, 3H, J = 6.0 Hz), 1.31 (d, 3H, J = 6.0 Hz), 1.5-2.4 (m, 2H), 2.95 (s, 3H), 3.3-4.1 (m, 2H), and 7.1-7.4 (m, 5H).

Anal. Calcd. for C₁₃H₁₈N₂O: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.22; H, 8.33; N, 12.94.

General Method of Preparation of 2,4-Diaminopentanes.

A solution of 3,4,5,6-tetrahydro-2(1H)pyrimidinone (I) (2 mmoles) in dry benzene (15 ml) was added to a well-stirred suspension of lithium aluminum hydride (20 mmoles) in dry tetrahydrofuran (15 ml). After refluxing for 20 hours, the reaction mixture was cooled, and the excess of lithium aluminum hydride was decomposed by slow addition of ethyl acetate and water. The precipitate was filtered off and then the filtrate was extracted with dichloromethane. The crude product was purified by column chromatography on silica gel with chloroform/acetate/ethanol/triethylamine (100:40:8:10) mixture, followed by vacuum distillation. Analytical data was summarized in Table 1 and Table 2.

3,4,6-Trimethyl-1-phenylhexahydropyrimidine (VI).

Method A.

Compound V was treated with lithium aluminum hydride according to the procedure for 2,4-diaminopentanes. The product VI was purified by column chromatography on silica gel with chloroform/acetone/ethanol (100:40:8) mixture, followed by vacuum distillation at 36°/10⁻⁴ mm Hg, 60% yield; ir: 2940, 1590, 1365, 1255, 750, and 690 cm⁻¹; nmr: δ 0.95 (d, 3H, J = 6.0 Hz), 1.13 (d, 3H, J = 6.0 Hz), 1.4-1.8 (m, 2H), 2.25 (s, 3H), 2.4-3.2 (m, 2H), 3.23 (d, 1H, J = 10 Hz), 3.90 (d, 1H, J = 10 Hz), and 7.0-7.4 (m, 5H).

Anal. Calcd. for C₁₃H₂₀N₂·O·1H₂O: C, 75.80; H, 9.82; N, 13.61. Found: C, 75.86; H, 9.91; N, 13.67.

Method B.

The mixture of compound IIa (2 mmoles) and 37% formaldehyde (6 mmoles) in benzene (25 ml) was stirred for 3 hours at room temperature. The reaction mixture was worked up according to method A.

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