An Asymmetric Synthesis of 2-Substituted Piperidines through Ozonolysis of Cyclopentenes and Reductive Aminocyclization

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By the action of ozone, sodium cyanoborohydride and the optically active benzylic amines **2**, the 1-substituted cyclopentenes **1**, **5** and **9** were converted to a diastereoisomeric mixture of 1,2-disubstituted piperidines (**3**, **6** and **10**), respectively. Hydrogenation of these compounds and the following work-up yielded optically active 2-alkylpiperidines (**4**, up to 68%*e.e.*), pipecolic acid (**7**, 84%*e.e.*) and 2-(hydroxymethyl)piperidine (**11**, up to 85%*e.e.*). Chromatographic separation of the major isomers of **3b** and **6** enabled optically pure coniine (**4b**) and pipecolic acid (**7**) to be prepared, respectively.

The applicability of sodium cyanoborohydride has been well appreciated for reductive alkylation of amines.¹⁾ The reagent has been utilized for reductive aminocyclization of dicarbonyl compounds, and selectively affords *cis*-2,6-disubstituted piperidines.²⁾ We have reported novel one-pot syntheses of morpholines and azacrown ethers, which involve reduction of ozonized dihydrofurans and subsequent reductive alkylation of amines by sodium cyanoborohydride.³⁾

This series of reactions could be applied to an asymmetric synthesis of 2-substituted piperidines from 1-substituted cyclopentenes when an optically active amine is employed. Thus we undertook syntheses of the optically active piperidines **4a**, **4b**, **7** and **11**, having methyl, propyl, carboxyl and hydroxymethyl groups, respectively. In the present work, chiral benzylic amines such as (*S*)-1-phenylethylamine (**2a**), (*R*)-1-(1-naphthyl)ethylamine (**2b**), (*R*)-

phenylglycine methyl ester (**2c**) and (*R*)-2-amino-2-phenylethanol (**2d**)⁴⁾ were chosen as nitrogen-atom donors, because their carbon-nitrogen bond could be cleaved easily by hydrogenation.

The 1-alkylcyclopentenes **1a** and **1b**⁵⁾ were treated successively with ozone and sodium cyanoborohydride. The aldehyde-ketones thus obtained were cyclized *in situ* with the optically active amines **2** by the action of the reducing agent to afford diastereoisomeric mixtures of the 1,2-disubstituted piperidines **3**. The carbon-nitrogen bond fission by hydrogenation over palladium hydroxide on carbon gave the 2-alkylpiperidines **4** (Scheme 1). The results of the asymmetric synthesis of **4** are presented in Table I. The *e.e.*'s of **4a** prepared by the use of **2a** and **2b** (entries 1 and 2) are higher than those of **4a** yielded by using **2c** and **2d** (entries 3 and 4). The reactivity of **2b** for **1a** was low and it took 6 days to complete the

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SCHEME 1. Asymmetric Syntheses of 2-Alkylpiperidines.

TABLE I. ASYMMETRIC SYNTHESES OF 2-ALKYLPYPERIDINES

Entry	Olefin	Amine		2-Alkylpiperidine				
		Compound	Config.	Compound	Overall yield (%)	Config.	[α] _D	<i>e.e.</i> (%)
1	1a	2a	<i>S</i>	4a	22	<i>S</i>	+5.3 ^{oa}	56
2	1a	2b	<i>R</i>	4a	19	<i>R</i>	-6.3 ^{oa}	67
3	1a	2c	<i>R</i>	—	—	—	—	20 ^c
4	1a	2d	<i>R</i>	4a	51	<i>S</i>	+0.3 ^{oa}	3
5	1b	2a	<i>S</i>	4b	30	<i>S</i>	+5.7 ^{ob}	39

^a [α]_D²⁴ -9.4° (*c*=0.95, EtOH); P. C. Wälichli *et al.*, *Helv. Chem. Acta*, **61**, 921 (1978).

^b [α]_D²³ +14.6° (neat); J. C. Craig and A. R. Pinder, *J. Org. Chem.*, **36**, 3648 (1971).

^c The *e.e.* was estimated from the ¹H NMR spectrum of the intermediate 1,2-disubstituted amine, which was obtained in a yield of 83%.

aminocyclization. The reaction with **1b** and **2b** was so slow that the corresponding 1,2-disubstituted piperidine (**3**) having propyl and 1-(1-naphthyl)ethyl groups could not be obtained in a practical yield.

The major isomer of the diastereomeric piperidine **3b** was successfully isolated by silica gel column chromatography. Hydrogenation of this compound afforded (*S*)-coniine (**4b**) of the natural form in a 73% yield whose specific rotation, [α]_D²⁵ +14.8° (neat), coincided with that reported, [α]_D²³ +14.6°.⁶⁾

By the same treatment of ozone, sodium cyanoborohydride and the amine **2a**, methyl 1-cyclopentenecarboxylate (**5**) was converted to a diastereoisomeric mixture of the amino ester **6** in a yield of 24% (Scheme 2).⁷⁾ Successive hydrogenation and alkaline hydrolysis of **6** yielded (*R*)-pipecolic acid (**7**) having [α]_D²¹ +20.4° (*c*=1.0, water), whose *e.e.* was calculated to be 83% based on a reported maximum rotation of [α]_D²³ +24.6° (*c*=3.35, water).⁸⁾ As to the maximum rotation of **7**, however, a

quite different value of [α]_D²⁰ -30.6° (*c*=1, water) has been presented.⁹⁾ Because the rotation method was considered to be unreliable for determining the *e.e.* of **7**, a determination based on the HPLC separation was realized. Racemic carbobenzyloxypipicollic acid was coupled with (*S*)-valine methyl ester to yield the fully protected dipeptide **8**. This sample gave two base-line separated peaks with equal areas (separation factor, α =1.10). Pipecolic acid (**7**) with [α]_D²¹ +20.4° was subjected to the analysis to exhibit a ratio of 92:8, and then the *e.e.* was calculated to be 84%.¹⁰⁾ The major diastereoisomer of the amino ester **6** was also separated by preparative thin-layer chromatography. The same treatment of hydrogenation and hydrolysis of the separated **6** afforded **7** having [α]_D²⁵ +24.0°. The HPLC analysis of the dipeptide **8** clarified that this sample was optically pure.

For the asymmetric synthesis of 2-hydroxymethylpiperidine (**11**), 1-(hydroxymethyl)cyclopentene (**9a**) and its derivatives

SCHEME 2. Asymmetric Synthesis of Pipecolic Acid.

SCHEME 3. Asymmetric Synthesis of 2-Hydroxymethylpiperidine.

TABLE II. ASYMMETRIC SYNTHESIS OF 2-HYDROXYMETHYLPIPERIDINE (11)

Entry	Olefin	Amine		2-Hydroxymethylpiperidine			
		Compound	Config.	Overall yield (%)	Config.	$[\alpha]_D^a$	<i>e.e.</i> (%)
1	9a	2a	<i>S</i>	45	<i>R</i>	-11.4°	71
2	9b	2a	<i>S</i>	58	<i>R</i>	-13.5°	84
3	9c	2a	<i>S</i>	81	<i>R</i>	-10.6°	66
4	9a	2d	<i>R</i>	36	<i>S</i>	$+6.2^\circ$	39

^a $[\alpha]_D^{21} - 16.0^\circ$ ($c = 2.34$, EtOH); H. Ripperger and K. Schreiber, *Tetrahedron*, **21**, 1485 (1965).

(**9b** and **9c**) were subjected to the reaction, and the 1,2-disubstituted piperidines **10** were obtained in a similar manner. Hydrogenation of **10a** gave 2-hydroxymethylpiperidine (**11**). The acyl group in **10b** was removed by alkaline hydrolysis prior to the hydrogenation. The yields, *e.e.*'s and configuration of **11** are shown in Table II. The protecting groups of the hydroxymethyl group in **9** did not affect the *ee* of **11** remarkably (entries 1~3).

As far as (*S*)-1-phenylethylamine (**2a**) was employed as a chiral auxiliary, the orientation of the substituents was identical throughout all the 2-substituted piperidines **4**, **7** and **11** prepared here. 2-Methylpiperidine (**4a**, Table I,

entry 1) and coniine (**4b**, Table I, entry 5) had the *S*-configuration and the others (**7** and **11**) had the *R*-configuration (Scheme 2; Table II, entries 1~3). The discrepancy is ascribed to the priority rule of the *R, S* notation, and those compounds actually have the same stereochemistry. This relationship between the configurations of the products and the amines (**2**) holds in the case of (*R*)-1-(1-naphthyl)ethylamine (**1b**, Table I, entry 2). The stereocourse of the present asymmetric synthesis can be rationalized by Scheme 4. The resulting aldehyde-ketone **12** from the cyclic olefin undergoes a reaction with the amine **2a** to form the amino-ketone **13**. This compound cyclizes to the iminium cation or the enamine

SCHEME 4. Presumable Stereocourse of the Present Asymmetric Aminocyclization.

whose probable conformation is depicted in **14** as the former form. When the cyanoborohydride ion attacks from the less-hindered site in which the methyl group orients, the configuration of the product leads to that shown in **15**.

EXPERIMENTAL

^1H NMR spectra were recorded in CDCl_3 with a Varian EM-360 spectrometer. Optical rotations were measured with a Perkin-Elmer R-241 polarimeter. HPLC analyses were carried out on a Jasco BIP-1 chromatographic system with a silica gel column (NUCLEOSIL 50-5, 4 mm $\times$ 25 cm); eluent, 3% 2-propanol in hexane, 0.5 ml/min, detecting at 254 nm. Elementary analyses were performed by a Yanaco MT-3 instrument. Distillation was performed with a Kugelrohr apparatus. 1-Methylcyclopentene (**1a**) and (*R*)-1-(1-naphthyl)ethylamine (**2b**) were purchased from Tokyo Kasei Corporation.

Asymmetric synthesis of (+)-2-methylpiperidine (4a); typical procedure for synthesizing 2-alkylpiperidines (4). Ozone gas was passed into a mixture of 1-methylcyclopentene (**1a**, 1.0 g, 12.2 mmol), MeOH (4.1 ml) and CH_2Cl_2 (20 ml) at -50°C , until a blue color developed, indicating consumption of the olefin. After removing the excess ozone with N_2 , NaBH_3CN (2.0 g, 31.8 mmol) was added to the solution, and the mixture was stirred at -50°C for 10 min. A solution of (–)-1-phenylethylamine¹¹ (**2a**, 1.5 g, 12.3 mmol) in acetonitrile (20 ml) was added dropwise, and stirring was continued at -30°C for 1 hr. Acetic acid (0.7 g, 12 mmol) in acetonitrile (10 ml) was added dropwise to the mixture at -30°C , and the mixture was stirred at -10°C overnight. After removing the solvents under reduced pressure, 10% NaOH (30 ml) was added. The mixture was extracted with CH_2Cl_2 (3 $\times$ 50 ml). The organic layer was washed with sat. NaCl and dried over Na_2SO_4 . After evaporation, the residue was distilled to give the product **3a** in a yield of 1.23 g (50%), bp $150\sim 155^\circ\text{C}/20$ mmHg. The 1,2-disubstituted piperidine (**3a**, 480 mg, 2.4 mmol) in EtOH (10 ml) was hydrogenated over $\text{Pd}(\text{OH})_2/\text{C}^{12}$ (200 mg) at ordinary

pressure for 4 hr. After filtering the catalyst, 3 N HCl (0.8 ml) was added to the solution. The mixture was evaporated, and the residue was dissolved in water (20 ml). After washing with ether (3 $\times$ 20 ml), the aqueous solution was made alkaline with 15% NaOH and extracted with ether (3 $\times$ 30 ml). The organic layer was washed with sat. NaCl and dried over Na_2SO_4 . After removing ether at ordinary pressure, the residue was distilled to give 2-methylpiperidine (**4a**) in a yield of 100 mg (43%), bp $90\sim 95^\circ\text{C}/130$ mmHg. $[\alpha]_D^{25} + 5.3^\circ$ ($c = 1.6$, EtOH). ^1H NMR δ : 0.8–2.0 (m, 6H, $(\text{CH}_2)_3$), 1.07 (d, $J = 6.4$ Hz, 3H, CH_3), 1.6 (broad s, 1H, NH), 2.3–3.3 (m, 3H, CH_2NCH). Picrate: mp $133\sim 134^\circ\text{C}$ (lit.¹³) $134\sim 135^\circ\text{C}$ for racemate, $116\sim 117^\circ\text{C}$ for *R*-form). *Anal.* Found: C, 43.82; H, 4.81; N, 17.08. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_7$: C, 43.91; H, 4.91; N, 17.07.

Asymmetric synthesis of (+)-coniine (4b). The disubstituted piperidine **3b** was prepared according to the typical procedure. Hydrogenation of **3b** afforded the product **4b** in a yield of 30% from **1b**, bp $110\sim 120^\circ\text{C}/100$ mmHg. $[\alpha]_D^{23} + 5.7^\circ$ (neat). ^1H NMR δ : 0.6–2.0 (m, 13H, $\text{CH}_2\text{CH}_2\text{CH}_3$, $(\text{CH}_2)_3$), 1.8 (broad s, 1H, NH), 2.1–3.3 (m, 3H, CH_2NCH). 3,5-Dinitrobenzamide: mp $80\sim 81^\circ\text{C}$. *Anal.* Found: C, 55.89; H, 5.91; N, 13.13. Calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_5$: C, 56.07; H, 5.96; N, 13.08.

Synthesis of optically pure (+)-coniine (4b). The disubstituted piperidine **3b** already prepared was subjected to silica gel column chromatography (25% EtOAc in hexane) to afford a diastereoisomer of **3b** in an overall yield of 43% from **1b**. $[\alpha]_D^{25} + 1.7^\circ$ ($c = 10.9$, EtOH). ^1H NMR δ : 0.7–1.1 (m, 3H, CH_2CH_3), 1.1–2.1 (m, 10H, $(\text{CH}_2)_3$ and $(\text{CH}_2)_2\text{CH}_3$), 1.23 (d, $J = 7.0$ Hz, 3H, CHCH_3), 2.1–3.0 (m, 3H, CH_2NCH), 4.04 (q, 1H, PhCH), 7.1–7.6 (m, 5H, aromatic protons). Hydrogenation yielded optically pure (+)-coniine (**4b**) in a yield of 73%. $[\alpha]_D^{25} + 14.8^\circ$ (neat).

Preparation of 1-cyclopentenecarboxylic acid and the methyl ester (5). A solution of NaOH (9.9 g) in water (41 ml) was added to a solution of AgNO_3 (21 g) in water (41 ml). The mixture was shaken, and 1-cyclopentenecarbaldehyde¹⁴ (6.0 g, 62 mmol) was added to it with ice-cooling. The mixture was shaken at room tempera-

ture for 20 min and filtered. The aqueous filtrate was made acidic with conc. HCl to deposit the product acid in a yield of 6.1 g (87%). The acid (5.0 g, 45 mmol) was heated in MeOH (50 ml) with conc. H_2SO_4 (1 ml) under reflux for 4 hr. After evaporation, the residue was dissolved in ether (100 ml). The solution was washed with sat. NaHCO_3 and sat. NaCl. Distillation gave the ester **5** in a yield of 4.2 g (75%), bp $85\sim 87^\circ\text{C}/25\text{ mmHg}$. ^1H NMR δ : 1.7~2.8 (m, 6H, $(\text{CH}_2)_3$), 3.69 (s, 3H, OCH_3), 6.5~6.8 (m, 1H, $=\text{CH}-$).

Asymmetric synthesis of (+)-pipecolic acid (7). Ozone gas was passed into a mixture of **5** (2.0 g, 15.9 mmol), MeOH (10 ml) and CH_2Cl_2 (20 ml) at 60°C , until a blue color developed. After removing the excess ozone with N_2 , NaBH_3CN (1.0 g, 15.9 mmol) and MeOH (10 ml) were added to the solution, and the mixture was stirred at -60°C for 30 min. A mixture of the amine **2a** (1.9 g, 15.7 mmol), acetic acid (0.9 g, 15.0 mmol) and MeOH (30 ml) was added to the solution at -60°C . Stirring was continued at 0°C for 15 hr. After removing the solvent under reduced pressure, sat. NaHCO_3 (30 ml) was added. The mixture was extracted with CH_2Cl_2 ($3\times 50\text{ ml}$). The organic layer was washed with sat. NaCl and dried over Na_2SO_4 . After evaporation, the residue was subjected to silica gel dry-column chromatography (40% EtOAc in hexane) to afford a diastereoisomeric mixture of the product **6** in a yield of 0.93 g (24%). The amino ester **6** (0.9 g, 3.6 mmol) in MeOH (50 ml) was hydrogenated over $\text{Pd}(\text{OH})_2/\text{C}$ (250 mg) at ordinary pressure for 2 hr. After filtering off the catalyst, evaporation gave an oil (0.53 g). This oil was dissolved in MeOH (2 ml) and treated with 6N NaOH (0.7 ml) at room temperature for 2 hr. Ion exchange resin of IR-120B (pyridine type) was added to neutralize the solution. After filtration, the solution was washed with CH_2Cl_2 (20 ml), and then evaporated. The residue was purified by sublimation at $200^\circ\text{C}/0.1\text{ mmHg}$ to afford **7** in a yield of 0.4 g (85%). $[\alpha]_D^{25} + 20.4^\circ$ ($c=1.0$, water). ^1H NMR (D_2O) δ : 1.3~2.6 (m, 6H, $(\text{CH}_2)_3$), 2.6~4.0 (m, 3H, CH_2NCH). Anal. Found: C, 55.42; H, 8.44; N, 10.70. Calcd. for $\text{C}_6\text{H}_{11}\text{NO}_2$: C, 55.80; H, 8.58; N, 10.84.

Synthesis of optically pure (+)-pipecolic acid (7). The amino ester **6** just prepared was subjected to silica gel preparative thin-layer chromatography (ptlc, 10% EtOAc in hexane) to afford a diastereoisomer of **6** in an overall yield of 22% from **5**. $[\alpha]_D^{25} - 15.9^\circ$ ($c=1.38$, EtOH). ^1H NMR δ : 1.1~2.2 (m, 6H, $(\text{CH}_2)_3$), 1.30 (d, $J=7.0\text{ Hz}$, 3H, CHCH_3), 2.2~3.0 (m, 2H, CH_2N), 3.75 (s, 3H, OCH_3), 3.7~4.0 (m, 1H, NCH), 3.95 (q, 1H, PhCH), 7.1~7.6 (m, 5H, aromatic protons). Successive hydrogenation and hydrolysis yielded optically pure (+)-**7** in a yield of 74%. $[\alpha]_D^{25} + 24.0^\circ$ ($c=1.04$, water).

Assessment of the e.e. of pipecolic acid (7) by HPLC.

Pipecolic acid (**7**, 42 mg, 0.33 mmol) was dissolved in 1N NaOH (0.73 ml). Benzyl chloroformate (61 mg, 0.36 mmol) was added, and the mixture was shaken with ice-cooling for 10 min and then at room temperature for 1 hr. The mixture was diluted with water (2 ml) and washed with ether ($3\times 1\text{ ml}$). The aqueous solution was made acidic with 6N HCl and extracted with EtOAc ($3\times 2\text{ ml}$). The organic layer was washed with sat. NaCl and dried over Na_2SO_4 . Evaporation gave carbobenzyloxypipecolic acid in a yield of 83 mg (97%). This compound (26 mg, 0.1 mmol) and (*S*)-valine methyl ester hydrochloride (17 mg, 0.1 mmol) were dissolved in CH_2Cl_2 (0.5 ml). DCC (21 mg, 0.1 mmol) and Et_3N (10 mg, 0.1 mmol) were added to the solution at 0°C . Stirring was continued at 0°C for 2 hr and then at room temperature for 2 hr. After filtering, evaporation gave the dipeptide **8** in a yield of 25 mg (66%). HPLC analysis was performed on the sample under the conditions already described.

Preparation of 1-cyclopentenemethanol (9a). 1-Cyclopentenecarbaldehyde (3.0 g, 31 mmol) was dissolved in MeOH (30 ml) and treated with NaBH_4 (0.8 g, 21 mmol) at 0°C for 1 hr. After adding water (50 ml), the mixture was extracted with CH_2Cl_2 ($4\times 30\text{ ml}$). The organic layer was washed with sat. NaCl and dried over Na_2SO_4 . Distillation gave the alcohol **9a** in a yield of 2.6 g (85%), bp $88\sim 89^\circ\text{C}/18\text{ mmHg}$ (lit¹⁵) bp $66/11\text{ mmHg}$. ^1H NMR δ : 1.5~2.5 (m, 6H, $(\text{CH}_2)_3$), 3.6 (broad s, 1H, OH), 4.1 (broad s, 2H, OCH_2), 5.4~5.6 (m, 1H, $=\text{CH}-$).

Preparation of the trimethylacetate (9b). The alcohol **9a** (2.9 g, 30 mmol) was dissolved in pyridine (27 ml) and treated with trimethylacetyl chloride (4.0 g, 33 mmol) at 0°C for 2 hr. After adding a few drops of water, the solvent was distilled off under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 ml). The solution was washed successively with 6N HCl, sat. NaHCO_3 and sat. NaCl, and then dried over Na_2SO_4 . Distillation gave the ester **9b** in a yield of 5.1 g (93%), bp $105\sim 110^\circ\text{C}/15\text{ mmHg}$. ^1H NMR δ : 1.22 (s, 9H, $(\text{CH}_3)_3$), 1.7~2.5 (m, 6H, $(\text{CH}_2)_3$), 4.5~4.7 (m, 2H, OCH_2), 5.5~5.7 (m, 1H, $=\text{CH}-$).

Preparation of the trimethylsilyl ether (9c). The alcohol **9a** (1.5 g, 15 mmol) was dissolved in a mixture of pyridine (1.3 ml) and CH_2Cl_2 (13 ml). Chlorotrimethylsilane (1.8 g, 17 mmol) was added to the solution at 0°C and stirring was continued at 0°C for 1 hr. After filtering, distillation gave the product **9c** in a yield of 2.1 g (83%), bp $90\sim 95/20\text{ mmHg}$. ^1H NMR δ : 0.21 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 1.6~2.6 (m, 6H, $(\text{CH}_2)_3$), 4.1~4.3 (m, 2H, OCH_2), 5.5~5.7 (m, 1H, $=\text{CH}-$).

Asymmetric synthesis of (–)-2-hydroxymethylpiperidine (11) from the ester (9b); typical procedure. Ozonolysis and aminocyclization were performed as described for the asymmetric synthesis of **7**. In the case using the esters **9a**

and **9c**, the following operation of hydrolysis was not necessary. The 1,2-disubstituted piperidine thus obtained (crude 2.7 g) from **9b** (1.7 g, 9.3 mmol) was hydrolyzed with 5% KOH in MeOH (50 ml) at room temperature overnight. After evaporation, water (50 ml) was added to the residue. The mixture was extracted with CH_2Cl_2 (2×50 ml), and the organic layer was washed with sat. NaCl and dried over Na_2SO_4 . Evaporation gave the amino alcohol **10** in a yield of 1.6 g (crude). Hydrogenation was carried out as described for **7** to afford the crude product as an oil (1.1 g). The oil dissolved in water (10 ml) was passed through a Sep-Pack C_{18} cartridge, and the cartridge was washed with water (10 ml). The combined aqueous solution was passed through IRA-400 ion-exchange resin (OH^- form, 20 ml), and the column was washed with water (30 ml). The combined eluent was concentrated under reduced pressure. Distillation gave the product **11** in a yield of 0.56 g (58%), bp $100 \sim 102^\circ\text{C}/2$ mmHg (lit.¹⁶) $98 \sim 102^\circ\text{C}/1$ mmHg). $[\alpha]_{\text{D}}^{20} -13.5^\circ$ ($c=2.38$, EtOH). ^1H NMR δ : 0.9~2.1 (m, 6H, $(\text{CH}_2)_3$), 2.3~3.2 (m, 3H, CH_2NCH), 3.2~3.7 (m, 2H, OCH_2), 3.9 (broad s, 2H, NH and OH). Picrate: mp $132 \sim 133^\circ\text{C}$ (lit.¹⁶) mp $135 \sim 137^\circ\text{C}$ for racemate, $102 \sim 105^\circ\text{C}$ for *R*-form). *Anal.* Found: C, 41.24; H, 4.57; N, 16.15. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_8$: C, 41.87; H, 4.68; N, 16.27.

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