Convenient Syntheses of 3,6-Dialkyl-1,4-dihydroxy-2,5-dioxopiperazines

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Some 3,6-dialkyl-1,4-dihydroxy-2,5-dioxopiperazines were conveniently prepared from the corresponding 3,6-dialkyl-2,5-dichloropyrazines *via* their 1,4-dioxides and 3,6-dialkyl-2,5-dihydroxypyrazine 1,4-dioxides. On the basis of the examination of pmr, tlc, and glc of the 2,5-dioxopiperazines derived from the products, it was clarified that all the products were *cis*-diastereomers.

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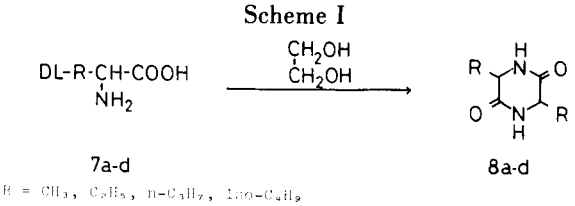
Hydroxamic acids occur frequently in nature, especially as mold metabolites, and are of interest biologically (1,2). Among such hydroxamic acids, the 1,4-dihydroxy-2,5-dioxopiperazine structure forms a part of mycelianamide, a metabolite of *Penicillium griseofulvum* Dierckx (3). Syntheses of some 1,4-dihydroxy-2,5-dioxopiperazines have been already achieved by ring closure (4,5). In the course of our works on pyrazines this paper reports convenient syntheses of several 3,6-dialkyl-1,4-dihydroxy-2,5-dioxopiperazines (**1a-d**) *via* 3,6-dialkyl-2,5-dichloropyrazine 1,4-dioxides (**4a-d**) starting from the corresponding dichloropyrazines (**2a-d**), as shown in Table I and II.

The oxidation of 3,6-dialkyl-2,5-dichloropyrazines (**2a-d**) was performed with six equivalents of potassium persulfate in concentrated sulfuric acid in the reported manner (6), to afford the 1-oxides (**3a-d**) and the 1,4-dioxides (**4a-d**), which were separated from each other by silica gel chromatography. Compounds **4a-d** were further converted to the corresponding dihydroxypyrazines (**5a-d**) by treatment with sodium methoxide in dioxan (7). The hydrogenation of 2,5-dihydroxypyrazine 1,4-dioxides (**5a-d**), thus obtained, was studied under various conditions. By the catalytic reduction over platinum dioxide the desired compounds (**1a-d**) were obtained in moderate yields. The products (**1a-d**) were purified by column chromatography on silica gel, and characterized by spectral and analytical data.

In order to determine the geometry of two alkyl groups, the products (**1a-d**) were reduced catalytically over Raney-Ni to the corresponding dioxopiperazines (**6a-d**), whose analytical data were compared with those of the dioxopiperazines (**8a-d**) prepared from the DL-amino acids (**7a-d**) (11).

Scheme I

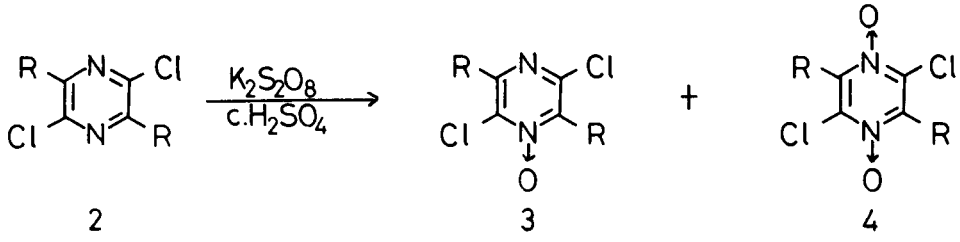


7a-d 8a-d

R = CH_3, C_2H_5, n-C_3H_7, iso-C_4H_9

Table I

Oxidation of 3,6-Dialkyl-2,5-dichloropyrazines

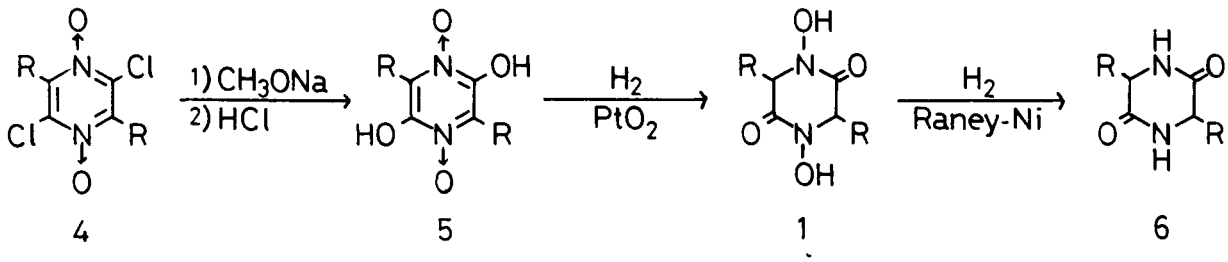


2 3 4

	Compound 2	Product 3	Yield (%)	Product 4	Yield (%)
2a	R = CH_3 (8)	3a (8)	61	4a (8)	19
2b	R = C_2H_5 (8)	3b (8)	39	4b (8)	58
2c	R = n-C_3H_7 (6)	3c (6)	74	4c (6)	26
2d	R = iso-C_4H_9 (9)	3d (7)	71	4d (7)	22

Table II

Syntheses of 1,4-Dihydroxy-2,5-dioxopiperazines and 2,5-Dioxopiperazines



4 5 1 6

Compound 4	Product 5	Yield (%)	Product 1	Yield (%)	Product 6	Yield (%)
4a R = CH_3	5a (10)	90	1a	38	6a	62
4b R = C_2H_5	5b	52	1b	27	6b	80
4c R = n-C_3H_7	5c	68	1c	20	6c	81
4d R = iso-C_4H_9	5d (7)	89	1d	32	6d	83

The pmr spectrum of 3,6-dimethyl-2,5-dioxopiperazine (**8a**) deduced from DL-alanine (**7a**) displayed two doublets at 1.66 and 1.72 ppm, due to the methyl protons of *trans*- and *cis*-isomers, respectively (12). On the other hand, the spectrum of 3,6-dimethyl-2,5-dioxopiperazine (**6a**) derived from 1,4-dihydroxy-3,6-dimethyl-2,5-dioxopiperazine (**1a**) exhibited a doublet at 1.72 ppm. Namely, this appearance suggested that **1a** was a *cis*-isomer. The pmr spectrum of 3,6-diethyl-2,5-dioxopiperazine (**6b**) was identical with the one of the *cis*-isomer (8).

The discrimination of the geometry of **6c** and **6d** could not be performed on the basis of pmr spectral data, because of difficulty to analyse the complicated spectra in the region between 1.00 and 4.00 ppm. Accordingly, thin layer chromatography (tlc) and gas-liquid chromatography (glc) of these compounds were examined.

The tlc of **8a** exhibited one spot under the reported conditions (12) and the one of **6a** indicated also a spot with the same Rf value as **8a**. On a tlc plate developed by the reported manner (13), the isobutyl compound (**8d**) indicated two spots (Rf = 0.54 and 0.68). Probably the former was the spot of the *cis*-isomer and the latter was the one of the *trans*-isomer, as described in the literature (13). Compounds **8b** and **8c** showed also two spots, respectively. On the other hand, **6b-d** indicated respectively one spot, and each was identical with the spots of the smaller Rf values due to **8b-d**. Rf values of *cis*-3,6-dialkyl-2,5-dioxopiperazines are smaller than those of the *trans*-isomers (13). Therefore one might conclude that the 2,5-dioxopiperazines (**6b-d**) were *cis*-isomers.

The glc of the trifluoroacetates (TFA's) of **6a-d** and **8a-d** supported also the conclusion presented above. According to Slater's work (14), the retention time of *trans*-3,6-dimethyl-2,5-dioxopiperazine-TFA is shorter than that of the *cis*-isomer-TFA on a 5% SE-30 column and the reverse is observed in the case of *cis* and *trans*-3,6-diisobutyl-2,5-dioxopiperazine-TFA's. In the present work, **8a**- and **8d**-TFA's showed respectively two peaks on the gas-liquid chromatogram using a 5% SE-30 column. The rear peak on the chromatogram of **8a**-TFA was identical with the one of **6a**-TFA. On the other hand, the front peak on the chromatogram of **8d**-TFA was identical with the one of **6d**-TFA. However, the geometrical isomers of **6b** and **6c** could not be discriminated by a 5% SE-30 column because **8b**- and **8c**-TFA's indicated merely one peak in each case.

Table III

TLC and GLC of 2,5-Dioxopiperazines

	6a	**8a**	**6b**	**8b**	**6c**	**8c**	**6d**	**8d**
tlc (Rf)	0.10	0.10	0.29	0.29 0.45	0.48	0.48 0.63	0.54	0.54 0.68
glc on 5% SE-30 (Rt, minutes)	9.1 (at 90°)	8.3 9.1 (at 90°)	5.8 (at 110°)	5.8 (at 110°)	11.8 (at 110°)	11.8 (at 110°)	5.6 (at 135°)	5.6 6.8 (at 135°)
glc on 5% OV-17 (Rt, minutes)	10.6 (at 100°)	10.6 (at 100°)	19.6 (at 100°)	19.6 21.6 (at 100°)	17.3 (at 110°)	17.3 19.0 (at 110°)	18.4 (at 110°)	18.4 25.6 (at 110°)

The glc using a 5% OV-17 column was effective to differentiate the retention times of TFA's of *cis*- and *trans*-dioxopiperazines (**8b-d**), except the case of **8a**-TFA. Compounds **8b**- and **8d**-TFA's showed two peaks, respectively. Among these peaks, the ones, which had a shorter retention time, were identical with the peaks of **6b**- and

6d-TFA's. Namely, the *cis*-diastereomers were eluted first. Compound **8c**-TFA showed also two peaks. The peak, which had a shorter retention time, may be due to the *cis*-isomer-TFA. Compound **6c**-TFA exhibited the peak with the same retention time as the one which had shorter retention time in the chromatogram of **8c**-TFA.

Conclusively, 1,4-dihydroxy-3,6-dialkyl-2,5-dioxopiperazines (**1a-d**) derived from 2,5-dichloro-3,6-dialkylpyrazines (**2a-d**) would be the *cis*-diastereomers.

EXPERIMENTAL

Melting points were recorded on a Yanagimoto micromelting point apparatus and are uncorrected. The uv spectra were recorded on a Hitachi 557 spectrophotometer, ir spectra on Shimadzu IR-400 spectrometer and pmr spectra on a Varian EM-360 instrument with tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi M-80 spectrometer.

The tlc of 2,5-dioxopiperazines was achieved on silica gel plates (Wakogel B-5) using a solvent system of a mixture (isopropyl ether-chloroform-acetic acid, 6:3:1). The chromatograms were developed by heating after spraying of sulfuric acid.

For glc, a Shimadzu Gas Chromatograph GC-4B equipped with FID was used. The glass column was packed with 5% SE-30 on Chromosorb W (Mesh 60-80, 4 mm × 1.5 m) and 5% OV-17 on Shimalite (Mesh 60-80, 4 mm × 3 m). As carrier gas nitrogen at 60 ml/minute was used. TFA's of 2,5-dioxopiperazines were prepared by the reported manner (14).

1) General Procedure for Preparation of 2,5-Dichloropyrazine 1,4-Dioxides (**4a-d**).

To a 2,5-dichloropyrazine (10 mmoles) dissolved in concentrated sulfuric acid (20 ml), potassium persulfate (30 mmoles) was added portionwise at room temperature in 30 minutes under stirring. After 24 hours, potassium persulfate (30 mmoles) was again added in the same way and the mixture was allowed to stand further for 24 hours. The reaction mixture was poured into ice water (60 ml) and extracted with chloroform. The chloroform layer was washed with 10% potassium bicarbonate and water, successively, and dried over sodium sulfate. After evaporation of chloroform *in vacuo*, the resulting oily residue was subjected to column chromatography on silica gel (Wakogel C-200, 20 g) to give a 1-oxide and a 1,4-dioxide, eluting with benzene and a benzene-ethyl acetate mixture.

2) General Procedure for Preparation of 2,5-Dihydroxypyrazine 1,4-Dioxides (**5a-d**).

To a suspension of sodium methoxide (100 mmoles) in dry dioxan (70 ml), a 2,5-dichloropyrazine 1,4-dioxide (10 mmoles) was added and heated at 110° for 4 hours. The solvent was evaporated off *in vacuo* and the residue was dissolved in water (20 ml). After the solution was washed with ether, the water layer was acidified with concentrated hydrochloric acid and the yellow precipitates were collected by suction.

Compound **5b**.

This compound was obtained as yellow prisms (methanol), mp 165-166°; ir (potassium bromide): 1580 (C=O) cm^{-1}; pmr (deuteriotrifluoroacetic acid): δ 1.30 (6H, t, J = 7 Hz, CH_2CH_3), 3.10 (4H, q, J = 7 Hz, CH_2CH_3) ppm; ms: m/e 200 (M^+), 183 (M^+-OH); uv (95% ethanol): λ max 207 (log ε 3.84), 235 (3.76), 284 (3.34), 340 (2.29), 384 (3.26), 424 (3.01) nm.

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.67; H,6.21; N, 13.61.

Compound **5c**.

This compound was obtained as yellow prisms (methanol), mp 149-150°; ir (potassium bromide): 1580 (C=O) cm^{-1}; pmr (deuteriotrifluoroacetic acid): δ 1.06 (6H, t, J = 7 Hz, $CH_2CH_2CH_3$), 1.77 (4H, m, $CH_2CH_2CH_3$), 3.09 (4H, t, J = 7 Hz, $CH_2CH_2CH_3$) ppm; ms: m/e 228 (M^+), 211 (M^+-OH); uv (95% ethanol): λ max 214 (log ε 3.91), 240 (3.85), 288 (3.52), 340 (3.08), 389 (3.53), 430 (3.13) nm.

Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.75; H, 7.18; N, 12.22.

3) General Procedure for Preparation of 1,4-Dihydroxy-2,5-dioxopiperazines (**1a-d**).

A suspension of a 2,5-dihydroxypyrazine 1,4-dioxide (10 mmoles) and platinum dioxide (50 mg) in methanol (150 ml) was placed in a bottle of Burgess-Parr reduction apparatus and shaken in an atmosphere of hydrogen under a pressure of 4 kg/cm^2 at *ca.* 40°, until the material was dissolved and the yellow color of the solution disappeared. After removal of the catalyst by filtration, the solvent was evaporated off *in vacuo*. The residue was purified by column chromatography on silica gel (Wakogel C-200, 20 g), eluting with chloroform and a mixture of chloroform-methanol (20:1).

Compound **1a**.

This compound was obtained as colorless needles (methanol), mp 240-241°; ir (potassium bromide): 1670 (C=O) cm^{-1}; pmr (deuteriotrifluoroacetic acid): δ 1.69 (6H, d, J = 6 Hz, $CHCH_3$), 4.53 (2H, q, J = 6 Hz, $CHCH_3$) ppm; ms: m/e 174 (M^+), 157 (M^+-OH); uv (95% ethanol): λ max 203 (log ε 3.83) nm.

Anal. Calcd. for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79; N, 16.08. Found: C, 41.61; H, 5.96; N, 16.12.

Compound **1b**.

This compound was obtained as colorless needles (methanol), mp 207-208°; ir (potassium bromide): 1660 (C=O) cm^{-1}; pmr (deuteriotrifluoroacetic acid): δ 1.01 (6H, t, J = 6 Hz, $CHCH_2CH_3$), 2.18 (4H, m, $CHCH_2CH_3$), 4.58 (2H, t, J = 4 Hz, $CHCH_2CH_3$) ppm; ms: m/e 202 (M^+), 185 (M^+-OH); uv (95% ethanol): λ max 203 (log ε 3.88) nm.

Anal. Calcd. for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.30; H, 7.05; N, 13.71.

Compound **1c**.

This compound was obtained as colorless needles (methanol), mp 184-185°; ir (potassium bromide): 1650 (C=O) cm^{-1}; pmr (deuteriotrifluoroacetic acid): δ 0.84 (6H, t, J = 7 Hz, $CHCH_2CH_2CH_3$), 1.25 (4H, m, $CHCH_2CH_2CH_3$), 1.93 (4H, m, $CHCH_2CH_2CH_3$), 4.42 (2H, t, J = 4 Hz, $CHCH_2CH_2CH_3$) ppm; ms: m/e 230 (M^+), 213 (M^+-OH); uv (95% ethanol): λ max 204 (log ε 3.85) nm.

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.37; H, 8.01; N, 12.18.

Compound **1d**.

This compound was obtained as colorless needles (methanol), mp178-180°; ir (potassium bromide): 1660 (C=O) cm^{-1}; pmr (deuteriotrifluoroacetic acid): δ 0.92 (12H, d, J = 6 Hz, $CHCH_2CH(CH_3)_2$), 1.84 (6H, m, $CHCH_2CH(CH_3)_2$), 4.47 (2H, t, J = 6 Hz, $CHCH_2CH(CH_3)_2$) ppm; ms: m/e 258 (M^+), 241 (M^+-OH); uv (95% ethanol): λ max 203 (log ε 3.94) nm.

Anal. Calcd. for $C_{12}H_{22}N_2O_4$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.78; H, 8.54; N, 10.85.

4) General Procedure for Catalytic Reduction of 1,4-Dihydroxy-2,5-dioxopiperazines (**1a-d**) to 2,5-Dioxopiperazines (**6a-d**).

A suspension of 1,4-dihydroxy-2,5-dioxopiperazine (1 mmole) and Raney-Ni, prepared from Ni-Al alloy (80 mg), in methanol (20 ml) was shaken under hydrogen until the calculated amount of the gas was taken up. After removal of the catalyst by filtration, the solvent was evaporated off *in vacuo*. The residue was purified by recrystallization.

Compound **6a**.

This compound was obtained as colorless needles (methanol), mp 292-294° [lit (15) mp 288-290°]; pmr (deuteriotrifluoroacetic acid): δ 1.72 (6H, d, J = 7 Hz, $CHCH_3$), 4.54 (2H, q, J = 7 Hz, $CHCH_3$) ppm.

Compound **6b**.

This compound was obtained as colorless needles (methanol), mp 244-246° [lit (8) mp 246-248°]; pmr (deuteriotrifluoroacetic acid): δ 1.08 (6H, t, J = 7 Hz, $CHCH_2CH_3$), 2.03 (4H, m, $CHCH_2CH_3$), 4.39 (2H, t, J = 4 Hz, $CHCH_2CH_3$) ppm.

Compound **6c**.

This compound was obtained as colorless needles (methanol), mp 258-260°; ir (potassium bromide): 1680 (C=O) cm^{-1}; pmr (deuteriotrifluoroacetic acid): δ 1.01 (6H, t, J = 6 Hz, $CHCH_2CH_2CH_3$), 1.49 (4H, m, $CHCH_2CH_2CH_3$), 1.91 (4H, m, $CHCH_2CH_2CH_3$), 4.38 (2H, t, J = 4 Hz, $CHCH_2CH_2CH_3$) ppm; ms: m/e 199 ($M^+ + 1$), 198 (M^+).

Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.28; H, 9.07; N, 14.08.

Compound **6d**.

This compound was obtained as colorless needles (methanol), mp 279-281° [lit (13) mp 270-271°]; pmr (deuteriotrifluoroacetic acid): δ 1.07 (12H, d, J = 5 Hz, $CHCH_2CH(CH_3)_2$), 1.87 (6H, m, $CHCH_2CH(CH_3)_2$), 4.38 (2H, t, J = 6 Hz, $CHCH_2CH(CH_3)_2$) ppm.

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