A Facile Synthesis of 3-(1-Benzyloxymethyl-3-hydroxypropyl)-2,5-piperazinedione

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Synopsis. The title compound, a key intermediate for a total synthesis of bicyclomycin, was obtained from γ-butyrolactone through eight steps in *ca.* 4.4% overall yield.

Bicyclomycin,[1] an antibiotic having unique structure[2] and biological activity, was recently synthesized in racemic[3] and optically active[4] forms. In these syntheses, the pathway in which the carbon-substituent is introduced into the 2,5-piperazinedione ring was adopted for the construction of racemic bicyclic skeleton. However, another pathway in which a precursor having a suitable carbon chain is cyclized into 2,5-piperazinedione[5] should be used for the synthesis of optically active skeleton, though many reaction steps are necessary. This paper describes a synthesis of racemic title compound (**12**) from γ-butyrolactone as an attempt of the latter pathway.

γ-Butyrolactone was converted into the racemic mixture of 2-methoxy-3-methoxycarbonyltetrahydrofuran (**1**) by the known method[6] in 82% yield. Reduction of **1** with lithium aluminum hydride (LAH) gave quantitatively the corresponding alcohol (**2**), which was converted into 3-benzyloxymethyl-2-hydroxytetrahydrofuran (**4**) in a good yield, by successive *O*-benzylation (**3**) and partial hydrolysis with 0.1 M (M=mol dm^{-3}) hydrochloric acid–dioxane (1:1) at room temperature.

Reaction of **4** in methanol with ammonia and hydrogen cyanide gave the corresponding amino nitrile (**5**) in 72% yield, and that with *p*-methoxybenzylamine instead of ammonia gave **6** in 85% yield. The structures of **5** and **6** were confirmed by ^{1}H NMR after conversion into acetates (**7** and **8**), respectively. While, the reaction of **4** with ammonium carbonate and sodium cyanide gave the corresponding hydantoin (**9**). However, the hydantoin ring could not be opened by refluxing with barium hydroxide for a long period. Hydrolysis of **5** in aqueous methanol with hydrochloric acid, and *N*-chloroacetylation of the product gave the expected product (**10**) and a lactone (**11**) in 23 and 31% yields, respectively. Successive treatment of **10** with sodium iodide for halogen exchange and with methanolic ammonia gave one of the two possible racemates of the corresponding 2,5-piperazinedione (**12**) as crystals in 24% yield. A similar treatment of **11** gave also **12** in 9% yield. The structure of **12** was confirmed by ^{1}H and ^{13}C NMR, after conversion into the corresponding *N,N',O*-triacetyl derivative (**13**).

Experimental

Melting points were determined with a Yanagimoto micro melting-point apparatus, and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JMN PS-100 and a JEOL FX-90Q spectrometers, respectively, in $CDCl_3$ with tetramethylsilane as the internal standard.

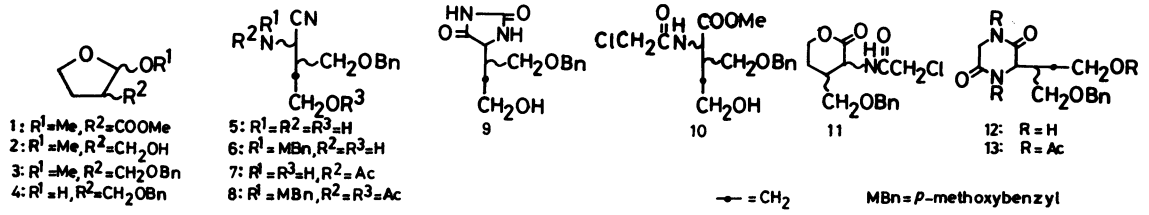
3-Hydroxymethyl-2-methoxytetrahydrofuran (2). Reduction of **1** (5.8 g, 39 mmol) in dry ether with LAH (3.0 g, 79 mmol) by the usual manner, and purification of the product on a column of silica gel (chloroform–hexane 3:1) gave **2** (5.1 g, 99%) as a syrup. ^{1}H NMR: δ 4.94 and 4.86 (each d, 1H, $J_{2,3}$=5.0 and 2.0 Hz, H-2), 4.05—3.65 (m, 2H, H-5), 3.54 (d, 2H, $J_{3,1'}$=8.0 Hz, CH_2OH), 3.36 (s, 3H, OMe), 2.7—1.8 (m, 4H, H-3,4 and OH). Anal. ($C_6H_{12}O_3$) C, H.

3-Benzyloxymethyl-2-methoxytetrahydrofuran (3). Benzylation of **2** (47.0 g, 350 mmol) in dry DMF with sodium hydride (18.8 g, 390 mmol) and benzylchloride (47.3 g, 370 mmol) by the usuel manner, and distillation of the product gave oily **3** (73.5 g) in 95% yield. Bp 119—125 °C/1 Torr (1 Torr=133.322 Pa). Anal. ($C_{13}H_{18}O_3$) C, H.

3-Benzyloxymethyl-2-hydroxytetrahydrofuran (4). Partial hydrolysis of **3** (5.0 g, 23 mmol) in dioxane (100 cm^3) with 0.1 M hydrochloric acid (100 cm^3) at room temperature for 2 days, and purification of the product on a silica-gel column (hexane–ethyl acetate 7:3) gave syrupy **4** (4.5 g, 96%). Anal. ($C_{12}H_{16}O_3$) C, H.

2-Amino-3-benzyloxymethyl-5-hydroxypentanenitrile (5). To a solution of **4** (10.0 g, 48 mmol) in abs methanol (80 cm^3) saturated with ammonia at 0 °C was added hydrogen cyanide (3.9 g, 144 mmol), the mixture was kept at room temperature for 72 h, and then evaporated. The residue was purified on a silica-gel column (chloroform–methanol 5:1) to give **5** (8.1 g, 72%) as a colorless syrup. The usual *N*-acetylation of **5** in methanol with acetic anhydride, and purification of the product on a preparative TLC (chloroform–ethyl acetate 1:1) gave syrupy 2-scetamido-3-benzyloxymethyl-5-hydroxypentanenitrile (**7**) in 89% yield. ^{1}H NMR: δ 7.35 (s, 6H, Ph and NH), 5.3—5.0 (m, 1H, H-2), 4.55 (s, 2H, CH_2Ph), 3.9—3.5 (m, 4H, H-5 and CH_2OBn), 2.70 (bs, 1H, OH), 2.45—2.15 (m, 1H, H-3), 1.93 and 1.87 [each s (1:1), 3H, Ac)], 1.9—1.5 (m, 2H, H-4). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

3-Benzyloxymethyl-5-hydroxy-2-(p-methoxybenzylamino)pentanenitrile (6). A similar treatment of **4** (2.3 g, 11 mmol) with hydrogen cyanide (0.90 g, 33 mmol) and *p*-methoxybenzylamine (1.7 g, 12 mmol) to **5**, and purification of the product on a silica-gel column (chloroform–methanol



7:1) gave **6** (3.3 g, 85%) as a colorless syrup. The usual acetylation of **6** in pyridine with acetic anhydride, and purification of the product on a preparative TLC (hexane–ethyl acetate 3:2) gave syrupy 5-acetoxy-3-benzyloxymethyl-2-[*N*-(*p*-methoxybenzyl)acetamido]pentanenitrile (**8**) in 65% yield. ^{1}H NMR: δ 7.42 and 7.39 (each s, 5H, Ph), 7.24, 7.16, 6.95 and 6.93 (each d, 4H, J=8.5 Hz, MBn), 5.45—5.15 (m, 1H, H-2), 4.9—3.4 (m, 6H, H-5, CH_2OBn and CH_2 in MBn), 4.54 and 4.52 (each s, 2H, CH_2Ph), 2.2—1.6 (m, 3H, H-3 and 4), 2.19 and 2.13 (each s, 3H, OAc), 2.04 and 2.01 (each s, 3H, NAc). Anal. ($C_{25}H_{30}N_2O_5$) C, H, N.

*5-(1-Benzyloxymethyl-3-hydroxypropyl)-2,4-imidazolidinedione (**9**).* A mixed solution of **4** (1.0 g, 4.8 mmol) in ethanol (40 cm^3), ammonium carbonate (4.3 g, 44.7 mmol) and sodium cyanide (0.48 g, 9.8 mmol) in water (40 cm^3), was heated for 5 h at 60 °C, poured into ice–water, and extracted with chloroform. The usual processing of the extract gave a crude syrup, which was purified on a column of silica gel (chloroform–methanol 9:1) to give **9** (540 mg) in 41% yield. ^{1}H NMR: δ 7.38 and 7.34 (each s, 5H, Ph), 4.78 (bs, 2H, NH and OH), 4.59 and 4.48 (each s, 2H, CH_2Ph), 4.28 and 4.40 (each d, 1H, $J_{3,1'}$=2.5 and 3.0 Hz, H-3), 3.8—3.5 (m, 2H, H-3′), 3.32 and 3.28 (each d, 2H, J=3.0 Hz, CH_2OBn), 2.6—2.2 (m, 1H, H-1′), 1.7—1.4 (m, 2H, H-2′). Anal. ($C_{14}H_{18}N_2O_4$) C, H, N.

*Methyl 3-Benzyloxymethyl-2-chloracetemido-5-hydroxypentanoate (**10**) and 3-Benzyloxymethyl-2-chloroacetamido-5-pentanolide (**11**).* A mixed solution of **5** (16.0 g, 68 mmol) in methanol (40 cm^3), methanol (40 cm^3) saturated at 0 °C with hydrogen chloride and water (2.4 g, 130 mmol) was kept at room temperature for 48 h, filtered, and the filtrate was evaporated to one third volume, again filtered, and the filtrate was evaporated. The usual *N*-chloroacetylation of the residue in benzene (120 cm^3) and ether (40 cm^3) with potassium carbonate (28.0 g, 203 mmol) in water (200 cm^3) and chloroacetyl chloride (15.4 g, 136 mmol) in benzene (20 cm^3) at 0 °C, and separation of the products on a column of silica gel (benzene–ethyl acetate 7:3) gave **11** (6.5 g, 31%) and **10** (5.5 g, 23%) as colorless syrups.

11: ^{1}H NMR: δ 7.56 and 7.16 (each d, 1H, $J_{2,NH}$=7.0 and 8.0 Hz, NH), 7.40 (s, 5H, Ph), 4.9—4.6 (m, 1H, H-2), 4.52 and 4.49 (each s, 2H, CH_2Ph), 4.45—4.25 (m, 2H, H-5), 4.07 and 3.97 (each s, 2H, CH_2Cl), 3.6—3.3 (m, 2H, CH_2OBn), 3.1—2.7 (m, 1H, H-3), 2.4—1.9 (m, 2H, H-4). Anal. ($C_{15}O_{18}O_4NCl$) C, H, N.

10: ^{1}H NMR: δ 7.86 and 7.75 (each bd, 1H, $J_{2,NH}$=8.0 and 7.0 Hz, NH) 7.35 (s, 5H, Ph), 4.9—4.7 (m, 1H, H-2), 4.44 (s, 2H, CH_2Ph), 4.27 and 4.25 (each t, 2H, $J_{4,5}$=6.5 Hz, H-5), 4.07 and 4.04 (each s, 2H, CH_2Cl), 4.05 (bs, 1H, OH), 3.71 (s, 3H, OMe), 3.6—3.3 (m, 2H, CH_2OBn), 2.6—2.2 (m, 1H, H-3), 2.0—1.7 (m, 2H, H-4). Anal. ($C_{16}H_{22}O_5NCl$) C, H, N.

*3-(1-Benzyloxymethyl-3-hydroxypropyl)-2,5-piperazinedione (**12**).* A solution of **10** (700 mg, 2.0 mmol) and 3 equimolar sodium iodide in acetone (20 cm^3) was refluxed for 3 h, evaporated to a half volume, poured into water, and then extracted with ethyl acetate. The usual processing of the extract gave a crude syrup, which was treated for 12 h at room temperature with methanol (10 cm^3) saturated with ammonia to give crude **12**. It was crystallized from methanol-ether and recrystallized from methanol–water. Yield, 24% (140 mg), mp 204—205 °C. Anal. ($C_{15}H_{20}N_2O_4$) C, H, N.

*3-[3-Acetoxy-1-(benzyloxymethyl)propyl]-1,4-diacetyl-2,5-piperazinedione (**13**).* The usual acetylation of **12** (100 mg, 0.34 mmol) in DMF (20 cm^3) with acetic anhydride (2 cm^3) and catalytic amount of 4-(dimethylamino)pyridine, and purification of the product on a column of silica gel (hexane–ethyl acetate 7:3) gave syrupy **13** (62 mg, 43%). ^{1}H NMR: δ 7.28 (s, 5H, Ph), 5.32 (d, 1H, $J_{3,1'}$=7.5 Hz, H-3), 4.97 (d, 1H, $J_{6a,6b}$=18.0 Hz, H-6a), 4.73 (s, 2H, CH_2Ph), 4.3—3.9 (m, 3H, H-6b and 3′), 3.6—3.35 (m, 2H, CH_2OBn), 2.54 and 2.51 (each s, 6H, NAc×2), 2.01 (s, 3H, OAc), 2.2—1.5 (m, 3H, H-1′ and 2′); ^{13}C NMR: 171.3s, 171.1s and 170.0s (C=O×3), 167.8s and 166.9s (C-2 and 5), 137.0s, 128.4d, 127.9d and 127.7d (aromatic), 73.4t, 69.5t and 61.4t (CH_2Ph, CH_2OBn and C-3′), 58.9d (C-3), 47.1t (C-6), 39.3d (C-1′), 28.3t (C-2′), 26.4q, 26.7q and 20.8q (Ac×3). Anal. ($C_{21}H_{26}N_2O_7$) C, H, N.

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