# SYNTHESIS AND CYCLIZATION OF 3-HYDROXYALKYLIDENE-2,5-PIPERAZINEDIONES (PDO) TO THE CORRESPONDING 3-SPIRO- AND 3,6-BRIDGED PDO DERIVATIVES

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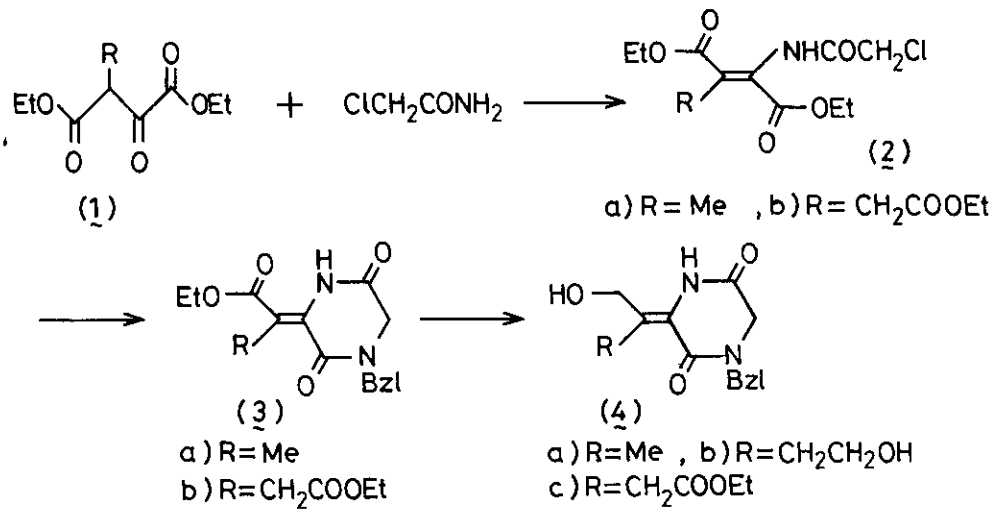
Abstract——Synthesis and cyclization of α-dehydroaspartate derivatives gave 3-hydroxyalkylidene-2,5-piperazinediones (PDO), which were then hydrogenated to give 3-hydroxyalkyl-PDO derivatives. Further cyclization of the two PDOs gave 3-spiro- and 3,6-bridged PDO derivatives.

In recent years, much attention has been directed to the synthesis of bicylomycin[1] containing a bicyclic structure of 2,5-piperazinedione (PDO) derivative. More recently, the chiral as well as achiral synthesis have been accomplished by three groups.[2-4] In these works, the cyclization of 3-(3-hydroxy)propyl-PDO derivatives to 3,6-bridged PDO is thought to be a main and the most important step.[5] Accordingly, it is of interest to investigate to what extent the similar cyclization of the other PDO derivatives can be applied. Here, we wish to report the syntheses of structurally interesting 3-spiro- and 3,6-bridged PDOs from α-dehydroaspartate derivatives by three or four steps respectively.

According to the method reported previosuly,[6] treatment of an equimolar ethyl oxalpropionate or oxalsuccinate (1: a; R=$CH_3$, b; R=$CH_2COOEt$) with chloroacetamide in benzene in the presence of $POCl_3$ and concentrated $H_2SO_4$ gave the expected ethyl 2-chloroacetylamino-3-ethoxycarbonyl-2-butenoate (2a: 158-160 °C/4 mmHg, 71%) and -2-pentenedionate (2b: 150-152 °C/4 mmHg, 48%) respectively. After the halogen exchange of 2a,b with KI by the usual method,[6] cyclization with benzylamine gave 1-benzyl-3-(2-ethoxycarbonyl-2-methyl)methylidene- and -3-(2,3-diethoxycarbonyl)-ethylidene-PDO (3a,b). Subsequent catalytic hydrogenation of 3a,b with $LiAlH_4$ in THF was performed, followed by the treatment with 1M-HCl. After removal of the insoluble substance, the filtrate was purified on a silica gel column using a




Scheme 1

mixture of $CHCl_3$ and acetone as the eluent to give 1-benzyl-3-(3-hydroxy-2-methyl)-ethylidene- and -3-(3,4-dihydroxy)sec-butylidene-PDO (4a,b). On the other hand, in the case of 3b with $NaBH_4$, the similar reduction of 2-ethoxycarbonyl group alone proceeded to give 1-benzyl-3-(3-ethoxycarbonyl-3-hydroxy)isopropylidene-PDO (4c) as an another reduction product. The yields, melting points, and spectroscopic data (IR and $^1$H-NMR) of 3 and 4 are summarized in Table 1. Moreover, 4b was subjected to the treatment with NBS in $CHCl_3$ in the absence of

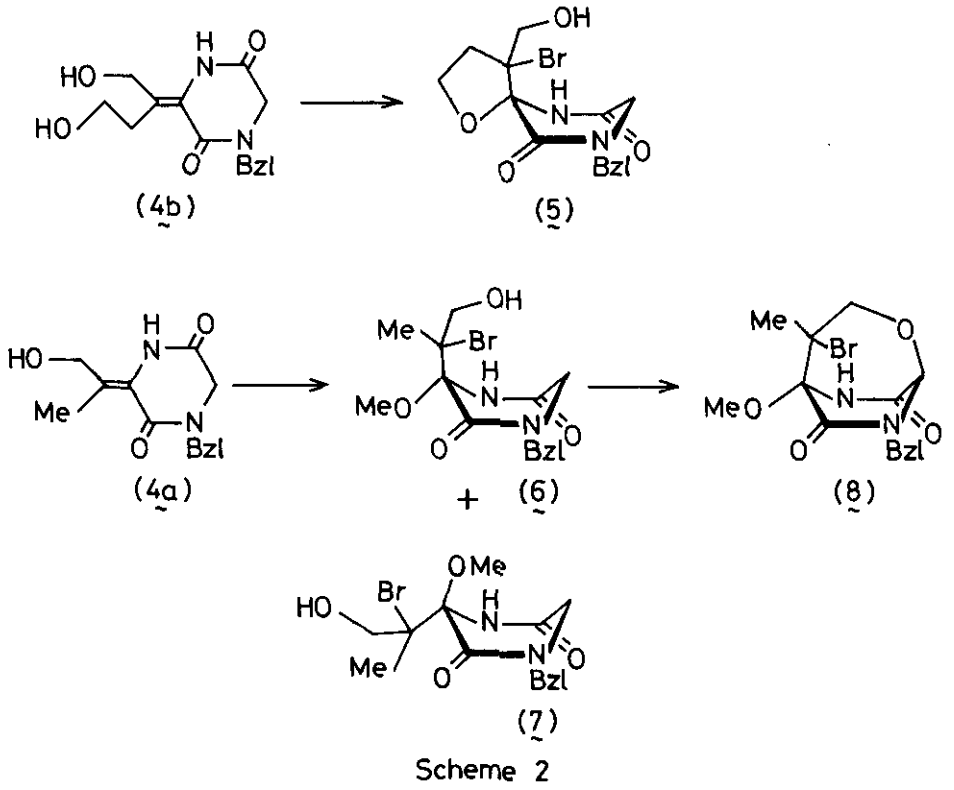
Table 1. 1-Benzyl-3-alkylidene-PDO Derivatives (3 and 4)

| Compd. No. | Yield (%) | Mp (°C) | IR (KBr), $cm^{-1}$ | | | | $^1$H-NMR, δ in $CDCl_3$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | OH | NH | C=O | C=C | OH | NH | $-CH_2-$[d] | R- |
| 3a | 75 | 123-124[a] | | 3170 | 1685 | 1620 | | 11.32bs | 3.96s | 2.18s[e] |
| 3b | 80 | 162-163[a] | | 3280 | 1740<br>1700<br>1665 | 1620 | | 11.30m | 4.03s | 4.15s[f] |
| 4a | 50 | 97-98[b] | 3400 | 3200 | 1670 | 1630 | 5.22t | 10.28bs | 3.92s | 2.11s[e] |
| 4b | 45 | syrup[c] | 3400 | 3220 | 1685<br>1660 | 1620 | 2.76m | 7.1-<br>7.7(Ph) | 4.32s | 3.5-[g]<br>4.8m |
| 4c | 40 | 149-151[b] | 3450 | 3170 | 1740<br>1710 | 1620 | 5.00m | 9.82bs | 3.32s | 3.1-[f]<br>4.0m |

a) Colorless needles from EtOH. b) Colorless needles from AcOEt. c) Colorless.
d) 6-Position of PDO. e) R=Me. f) R=$CH_2$COOEt. g) R=$CH_2CH_2$OH.

alcohol. As a result, it was found that, even in the presence of two hydroxyalkyl moieties, only 3-hydropropylidene group cyclized predominantly to give 1-benzyl-3-(4-bromo-4-hydroxy-1-oxy)cyclopentylspiro-PDO (5).

On the other hand, treatment of 4a with NBS in methanol was similarly worked up to give 1-benzyl-3-methoxy-3-(1-bromo-2-hydroxy-1-methyl)ethyl-PDO (6 and 7) as a mixture of two chemical spieces, which could be purely separated by the recrystallization method. In order to confirm the conformational structure, the diastereomer thus obtained was then attempted individually to the cyclization, according to the procedure reported by us.[5] As a result, firstly crystallized 6 was readily cyclized by NBS in $CHCl_3$ to give colorless needles, which were identified as 7-benzyl-4-bromo-5-methoxy-4-methyl-7,9-diaza-2-oxabicyclo[3.2.2]nonan-6,8-dione (8). While, even by the similar way as above, the secondly crystallized 7 from the filtrate were found to be never cyclized but to be only recovered. Judging from the above results, the compound 6 could be confirmed to have a folding structure between PDO ring as a boat type[5] and 3-hydroxyalkyl group, whereas 7 seems to be a linear molecule regarding the above two moieties, as is




Scheme 2

illustrated in Scheme 2.

The yields, melting points, and spectral data of 5-8 are summarized in Table 2.

Table 2. Various PDO Derivatives (5-8)

| Compd. No. | Yield (%) | Mp (°C) | IR (KBr), $cm^{-1}$ NH | (OH) | C=O | | $^1$H-NMR, δ in $CDCl_3$ NH[OH](Hz) | $-CH_2-$(Hz)[e)] | R- |
|---|---|---|---|---|---|---|---|---|---|
| 5 | 75 | 178-180[a)] | 3180 | (3330) | 1680 | 1665 | 8.50bs [5.26t] (6.0) | 3.92ABq (13.0) | 3.6-4.3m |
| 6 | 81 | 140-141[b)] | 3220 | (3430) | 1675 | 1655 | 7.69bs [3.60m] | 3.94ABq (18.0) | 1.78s |
| 7 | | 147-148[b)] | 3210 | (3425) | 1680 | 1660 | 7.68bs [4.08m] | 3.98ABq (14.0) | 1.86s |
| 8 | 99 | 169-170[c)] | 3220 | | 1725 | 1710 | 8.35bs | 5.02s[f)] | 1.69s |

a) Colorless needles from $CHCl_3$. b) Colorless needles from AcOEt. c) Colorless needles from $CCl_4$. e) methylene in PDO ring. f) >CH-O- in PDO ring.

In the IR and $^1$H-NMR spectra, disappearance of absorption band of C=C bond of 4b at 1620 $cm^{-1}$ and that of OH group of 6 at 3430 $cm^{-1}$ and appearance of methine proton signal of 8 at δ 5.02 as singlet indicate unambiguously the formation of spiro-PDO (5) and 3,6-bridged PDO respectively. Moreover, the structure of all new products (3-8) were supported by the spectroscopic data and satisfactory results in elemental analysis.

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