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FACILE SYNTHESES OF 3-SPIRO- AND 3,6-BRIDGED 2,5-PIPERAZINEDIONES

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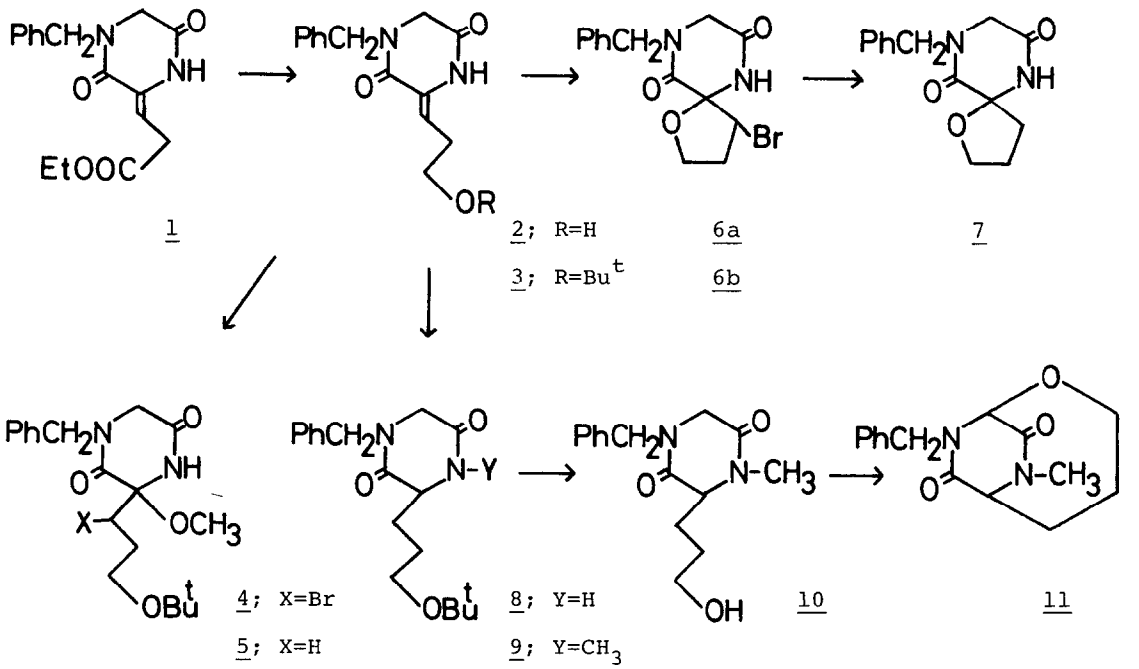
Summary: The intramolecular addition of hydroxyl group of 3-(3-hydroxyl)propylidene-2,5-piperazinedione to 3-position and the same substitution of 3-(3-hydroxy)propyl derivative to 6-position gave the corresponding 3-spiro- and 3,6-bridged 2,5-piperazinediones, respectively.

Recently, much attention is being denoted to the synthesis of fumitremorgins,[1] verruculogen,[2] and bicyclomycin,[3] containing a hydroxyl group at 3-position and a bicyclic structure of 2,5-piperazinedione (PDO) derivatives. In connection with the synthesis of α-alkoxy-α-amino acids,[4] more recently, the convenient and facile addition of alcohols and water to the C=C bond of 3-alkylidene- and 3,6-dialkylidene-PDO has been presented by us.[5] On the other hand, concerning the preparation of 3-alkoxy-PDO, the similar addition reaction[6] and the another preparative method have been reported.[7,8] Here, we wish to report the more applicable intramolecular addition and substitution of 3-(3-hydroxy)propylidene- and -propyl-PDO, whose results are devoted to the suggestion for the synthesis of the bicyclic structural skeleton of bicyclomycin.

As the starting 3-alkylidene-PDO, ethyl 2-chloroacetylamino-4-ethoxycarbonyl-2-butenoate [Bp 162-164 ^{o}C/2mmHg. IR: 3300 (NH), 1740 (COOEt), 1690 and 1520 (NHCO) cm^{-1}. NMR: δ 6.94, 7.36t (-CH=, J=7.0Hz), 8.28, 8.66 (NH)], derived by the condensation of ethyl 4-ethoxycarbonyl-2-oxobutanoate with chloroacet-

amide,[9] was cyclized with benzylamine to give the expected 1-benzyl-3-(2-ethoxycarbonyl)ethylidene-PDO [1; yield 64%, mp 131-132 °C. IR: 3200, 1735, 1685, 1635 cm^{-1}. NMR: δ 6.30t (-CH=, J=7.5Hz), 9.76 (NH)]. The subsequent reduction of 1 with $LiAlH_4$ in THF by the usual way gave 1-benzyl-3-(3-hydroxy)propylidene-PDO as colorless crystals [2; yield 60%, mp 130-131 °C. IR: 3400, 3200, 1680, 1630 cm^{-1}. NMR: δ 6.25t (-CH=, J=8.0Hz), 3.76 (OH), 9.62 (NH)]. After preparation of 3-(3-t-butoxy)propylidene-PDO [3; yield 88%, mp 123-125 °C. IR: 3180, 1680, 1635 cm^{-1}. NMR: δ 6.28 (-CH=, J=8.0Hz), 9.56 (NH)] from 2 and isobutene, the reaction of equimolar 3 (2.85 mmol) with N-bromosuccinimide (NBS) in MeOH (10 ml) proceeded to give colorless crystals, identified as 1-benzyl-3-methoxy-3-(3-t-butoxy-1-bromo)propyl-PDO [4; δ 4.94t (-CHBr-, J=5.5Hz)]. Subsequently, the hydrogenation of 4 with 10% Pd-C in the presence of Et_3N gave the corresponding 3-t-butoxypropyl-PDO [5; δ 2.06m ($-CH_2-$)].



1 — 2; R=H, 3; R=Bu^t — 6a, 6b — 7

4; X=Br, 5; X=H — 8; Y=H, 9; Y=CH_3 — 10 — 11

On the other hand, for the purpose of the intramolecular addition of hydroxyl group, equimolar 2 (3.08 mmol) was subjected to the treatment with NBS in $CHCl_3$ (20 ml) to give a syrupy substance, which was found to be consisted of two chemical species as a diastereomer. The two isomers were separated readily

by chromatography on a silica gel column using a mixture of $CHCl_3$-acetone (25 : 1 v/v) as the eluent to give two kinds of colorless crystals, which were identified as 3-(4-bromocyclopentyl-1-oxy)spiro-PDO [6a; δ 5.05t (-CHBr-, J=7.5Hz)] from first fraction and the diastereoisomer [6b; δ 4.22m (-CHBr-)] from the second, respectively. Subsequently, the bromine of each isomer thus obtained was debrominated with 10% Pd-C in the presence of Et_3N by the catalytic reduction to give the corresponding same spiro-PDO derivative [7; δ 2.02m (-CH_2- at 4-position)] in a fairly good yield.

Furthermore, in order to synthesize the desired 3,6-bridged PDO derivative, successive reduction of 3 with 10% Pd-C to the corresponding saturated PDO [8; δ 4.02m (3-H)] and the methylation of 8 with methyl iodide to the corresponding N-methylated PDO [9; δ 4.03t (3-H, J=5.5Hz)] were carried out by the usual methods, followed by the removal of t-butyl group by CF_3COOH to give 1-benzyl-3-(3-hydroxy)propyl-4-methyl-PDO [10; 3350 (OH), 1660 (CO) cm^{-1}, δ 4.40 (OH), 4.04t (3-H, J=5.0Hz)] in an 83% overall yield from 3. Subsequently, a solution

Table 1. The yields, melting points, and spectral data of 4-9, and 10

Compound No.	Yield (%)	Mp °C[c]	NMR spectrum, δ in $CDCl_3$ NH	6-H (J_{Hz})	IR spectrum[f] (cm^{-1}) NH
4	96	138	8.54	3.94d (1.5)	3170
5	95	syrup	8.34	3.89q (18.0)[e]	3220
6a	59	142-143	7.92	3.91q (18.0)[e]	3270
6b	25	150-151	8.30	3.88d (4.0)	3180
7	91[a] 90[b]	94-95	8.79	3.89q (18.0)[e]	3200
8	92	120-122	7.74	3.77s	3240
9	98	97-98	—	3.83q (18.0)[e]	—
10	92	73-75[d]	—	3.86d (2.5)	—

a) From 6a. b) From 6b. c) Colorless needles. d) Colorless prisms. e) AB quartet. f) In KBr.

of equimolar 10 (3.99 mmol) and NBS in $CHCl_3$ (10 ml) was refluxed for about 1 hour and then the reaction solution was washed twice with water. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated to give colorless

crystals, which was identified as 8-benzyl-10-methyl-8,10-diaza-2-oxobicyclo-[4.2.2]decan-7,9-dione [11; yield 68%, mp 136-138 °C. IR: 1670 (CO) cm^{-1}. NMR: δ 4.12dd (3-H, J=3.0Hz and J=4.5Hz), 5.12s (6-H)].

In consequence, it could be first generallized the inter- and intramolecular addition of hydroxyl group in the presence of NBS to 3-alkylidene-PDO and the intramolecular substitution to 6-position giving the corresponding 3-alkoxy-, 3-spiro-, and 3,6-bridged PDO.

From the above results, the formation mechanism of 4 and 6 is presumed that the N-bromo derivative of 3 and 2 is initially formed as an intermediate, followed by the 1,3-migration of the bromine to yield unstable intermediate containing C=N bond in ring, to which hydroxyl group immediately adds to give 4 and 6. In fact, when the nitrogen atom was protected with acyl group, the addition of hydroxyl group to C=C bond did not proceed.[5,10] On the other hand, in the case of 10, it is supposed that bromine attacked initially to the ring methylene at 6-position of 10 to form 1-benzyl-6-bromo-4-methyl-3-(3-hydroxy)propyl-PDO as an unstable intermediate, in which the subsequent cyclization between the bromo and hydroxylpropyl groups by the nucleophilic substitution proceeds to give 11.

References

1) M. Yamazaki, S. Suzuki, and K. Miyaki, Chem. Pharm. Bull. (Tokyo), 19, 1739 (1971).
2) J. Fayos, D. Lokensgard, J. Clardy, R. J. Cole, and J. W. Kirksey, J. Am. Chem. Soc., 96, 6785 (1974).
3) T. Miyoshi, N. Miyairi, H. Aoki, M. Kohsaka, H. Sasaki, and H. Imanaka, J. Antibiotics, 25, 569 (1972).
4) C. Shin, Y. Sato, and J. Yoshimura, Bull. Chem. Soc. Jpn., 49, 1909 (1976).
5) C. Shin, Y. Sato, T. Takada, K. Hibi, and J. Yoshimura, 42nd National Meeting of the Chemical Society of Japan, Sendai, September 1980, Abstr. II, p. 584.
6) J. D. M. Herscheid, R. J. F. Nivard, M. W. Tijhuis, H. P. H. Scholten, and H. C. J. Ottenheijm, J. Org. Chem., 45, 1880 (1980).
7) L. V. Dunkerton and R. M. Ahmed, Tetrahedron Lett., 1980, 1803.
8) M. Maag, J. F. Blount, D. L. Coffen, T. V. Steppe, and F. Wong, J. Am. Chem. Soc., 100, 6786 (1978).
9) C. Shin, Y. Fujii, and J. Yoshimura, Tetrahedron Lett., 1971, 2499.
10) Unpublished data.

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