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Syntheses of Picroroccelin Diastereomers and Their Regioisomers

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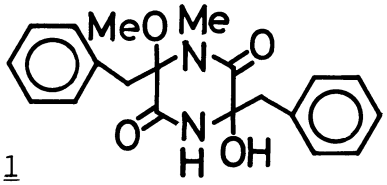
Picroroccelin, 3,6-dibenzyl-3-hydroxy-6-methoxy-1-methyl-2,5-piperazinedione, and its regioisomer were synthesized as the diastereomeric mixtures from glycine anhydride via 3,6-dibenzylidene-1-methyl-2,5-piperazinedione by eight steps.

After about sixty years, recently, the structure of picroroccelin,[1] a bitter substance isolated from lichen Roccella fuciforms,[2] was revised to 3,6-dibenzyl-3-hydroxy-6-methoxy-1-methyl-2,5-piperazinedione (1).[3] Interestingly, the natural product has an unsymmetrical 2,5-piperazinedione (PDO) structure and seems to have been derived by the oxidation of symmetric 3,6-dibenzylidene-PDO, which is also a naturally occurring product.[4,5] However, unfortunately, not only the spectral data but also the conformational determination of 1 has not yet been reported, ecept for its melting point and specific rotation.



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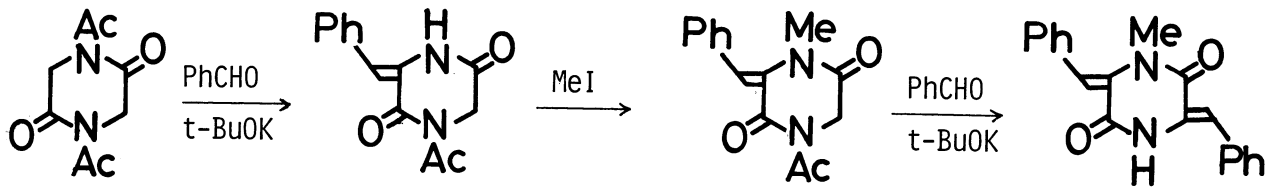
Previously, we reported the useful alkoxylation and hydroxylation of exocyclic C=C bond by using N-bromosuccinimide (NBS) as well as the selective methylation of 1- and 4-positions of PDO.[6-9] Here, we wish to report the facile synthesis of many unsymmetric 3- or 6-monosubstituted and 3,6-disubstituted PDO and achiral picroroccelin derivatives from 1,4-diacetyl-PDO (2).

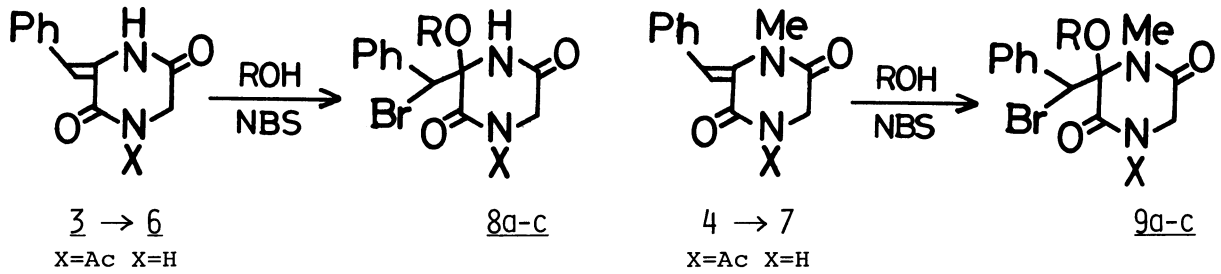
3,6-Dibenzylidene-1-methyl-PDO (5), seemed to be the most promising starting material for 1, was obtained by the condensation of 1-acetyl-3-benzylidene-4-methyl-PDO (4), derived from 2 and benzaldehyde via 1-acetyl-3-benzylidene-PDO (3)[10] [5; yield 98%, mp 181-182 °C. IR (KBr): 1680 (C=O), 1620 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.16 and 7.01 (s, 1H, -CH=), 2.94 (s, 3H, $-CH_3$)]. Prior to the reaction of 5 thus obtained, the elimination of acetyl group by the treatment of 3 and 4 with hydrazine hydrate by the usual method gave 3-benzylidene-PDO and 6-benzylidene-1-methyl-PDO (6 and 7) in good yields. Moreover, we examined the



2 3 4 5

Scheme 1.

absence or presence of 1-methyl group in 6 and 7 respectively affected to what extent the addition of alcohol or water to C=C bond, according to the procedure reported previously.[7] As a result, by comparing with the both reactivities under same conditions, the conversions of 3 and 6 (5 min) to the corresponding 3-alkoxy- and 3-hydroxy-3-α-bromobenzyl-PDO (8a-c) were found clearly to be very faster than those of 4 and 7 (1 h) to the similar 1-methyl-PDO (9a-c). Consequently, it is presumed that, in the case of 5, the analogous addition will take place predominantly on the benzylidene site in the absence of the vicinal methyl group. Schemes 1 and 2 and Table 1 summarize the results.



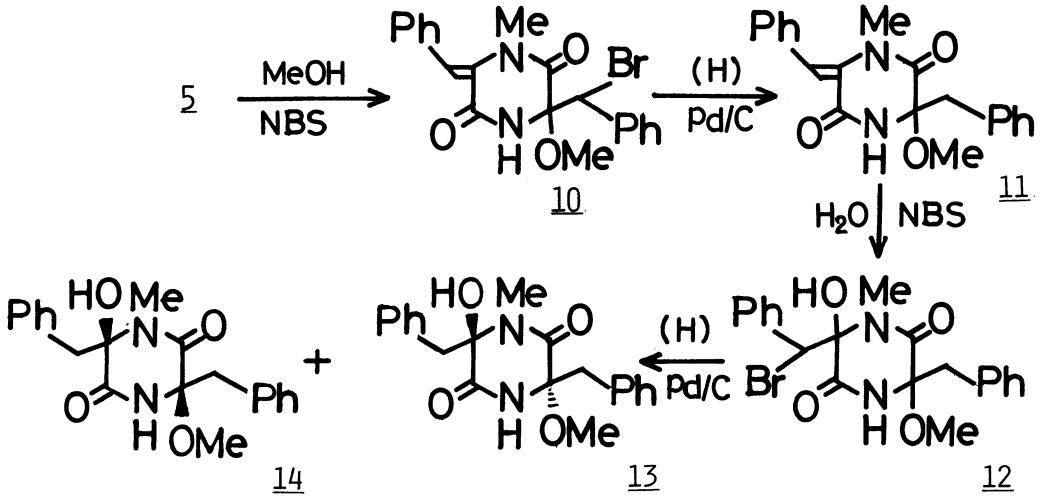
3 → 6 (X=Ac X=H) 8a-c 4 → 7 (X=Ac X=H) 9a-c

Scheme 2. a; R=X=H, b; R=Me, X=H, c; R=Me, X=Ac

Table 1. Yields, melting points, and spectral data of 8 and 9

Compd. No.	Yield %	Mp/°C	^{1}H-NMR, δ ($CDCl_3$) -CHBr-	-OH(OMe)	Compd. No.	Yield %	Mp/°C	^{1}H-NMR, δ ($CDCl_3$) -CHBr-	-OH(OMe)
8a	94	168-169	5.38s 5.40s	3.82bs	9a	81	169-170	5.40s 5.50s	3.64bs
8b	75	164-165	5.35s	(3.08s) (3.14s)	9b	77	158-159	5.24s	(3.02s)
8c	92	148-149	5.48s	(4.14s)	9c	98	115-116	5.30s	(3.24s)

In fact, the reaction of 5 (16.5 mmol) with MeOH (30 ml) in the presence of NBS (16.4 mmol) in chloroform (90 ml) at room temperature for 1 h took place to give the corresponding 3-α-bromobenzyl-3-methoxy-PDO derivative [10; yield 90%, mp 165-166 °C. IR: 1690 (C=O), 1630 (C=C) cm^{-1}. ^{1}H-NMR: δ 9.62 (bs, 1H, NH), 6.85 (s, 1H, -CH=), 5.42 (s, 1H, -CHBr-), 2.52 (s, 3H, $-OCH_3$)], followed by the catalytic hydrogenolysis with 10% Pd/C in the presence of triethylamine. As a result, 3-benzyl-6-benzylidene-3-methoxy-1-methyl-PDO was obtained quantitatively [11; mp 154-155 °C. IR: 1620 (C=C), 1080 (OCH_3) cm^{-1}. ^{1}H-NMR: δ 6.85 (s, 1H, -CH=), 3.22 (s, 3H, $-OCH_3$)]. Furthermore, the similar reaction of 11 with water gave 3-benzyl-6-α-bromobenzyl-6-hydroxy-3-methoxy-1-methyl-PDO (12) in an almost quantitative yield, followed by the hydrogenolysis. Consequently, 3,6-dibenzyl-6-hydroxy-3-methoxy-1-methyl-PDO thus obtained as a regioisomer of 1 was found to be a mixture of two diastereoisomers (13 and 14), as shown in Scheme 3 and Table 2.



Scheme 3.

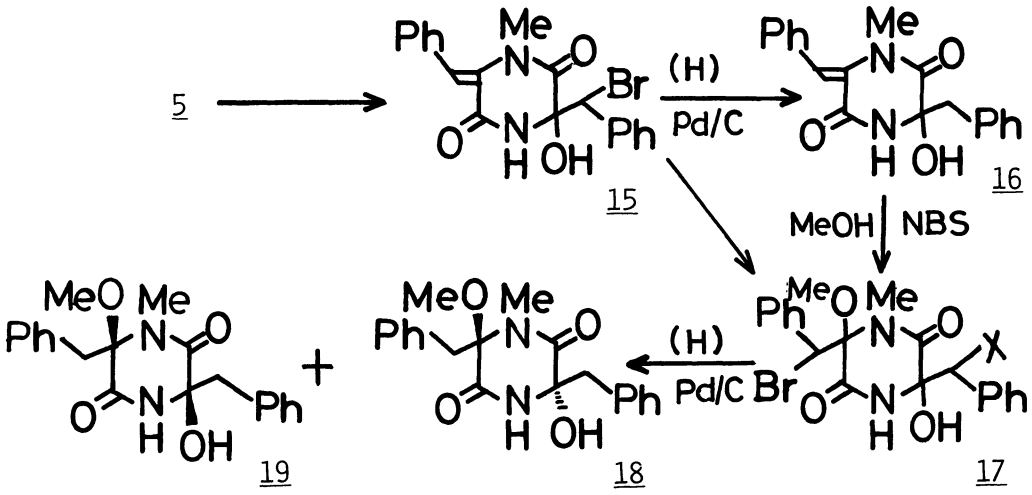
Table 2. 3,6-Dibenzyl-3,6-disubstituent-PDO derivatives

Compd. No.	Yield %	Mp/°C	^{1}H-NMR, δ (DMSO-d_6) -CHBr-	N-Me(OMe)	Compd. No.	Yield %	Mp/°C	^{1}H-NMR, δ (DMSO-d_6) -CHBr-	N-Me(OMe)
12	98	77-78	4.36s 4.78s	2.58s (2.97s)	17b	70	152-155	4.07s 5.56s	2.57s (3.08s)
13) 14	77	103-104	——	2.80s (3.00s)	18) 19	60	167-168	——	2.78s (3.05s)
17a	90	59-60	5.08s 5.10s	2.90s (3.08s)	N.P.[a]		192-194	([α]$_D$=+12.5°	

a) N.P. = Natural product.

On the other hand, the similar reaction of 5 with water was also achieved to give 6-benzylidene-3-α-bromobenzyl-3-hydroxy-1-methyl-PDO [15; yield 95%, mp 146-147 °C. IR: 3250 (OH), 1630 (C=C) cm^{-1}. ^{1}H-NMR: δ 6.84 (s, 1H, -CH=), 5.37 (s, 1H, -CHBr-), 2.80 (bs, 1H, OH)], followed by the hydrogenolysis [16; yield 88%, mp 149-150 °C. IR: 3430 (OH), 1630 (C=C) cm^{-1}. ^{1}H-NMR: δ 6.86 (s, 1H, -CH=), 3.38 (bs, LH, -OH)]. In addition, it was found that the compound 16 thus obtained was also succeeded in the similar addition of MeOH to give the corresponding 6-α-bromobenzyl-6-methoxy-PDO derivative (17a). However, because of tedious stepwise hydrogenolysis, the another direct and one-pot treatment was chosen.

Treatment of 15 (7 mmol) with MeOH (30 ml) in the presence of NBS (7 mmol) in chloroform (90 ml) at room temperature for 3 h was carried out to give the corresponding 3,6-di(α-bromobenzyl)-3-hydroxy-6-methoxy-1-methyl-PDO (17b), which was subsequently hydrogenolyzed with 10% Pd/C in the presence of triethylamine in ethyl acetate at room temperature for 30 min to give the expected 3,6-dibenzyl-3-hydroxy-6-methoxy-1-methyl-PDO (18 and 19) as diastereomeric mixtures in good yields. Recrystallization of the crystalline mixtures from petroleum ether gave



Scheme 4.

18 or 19 as colorless needles. The structure of the product thus obtained was supported by the spectroscopic data [IR: 3250-3400 (NH and OH) cm^{-1}. ^{1}H-NMR: δ 8.46 (s, 1H, -NH-), 6.66 (s, 1H, -OH)] and the satisfactory result in elemental analysis.

In conclusion, it is noteworthy that the different two kinds of unsymmetric PDO derivatives were readily synthesized by using 5, while only symmetric 3,6-dimethoxy-PDO was obtained by using 3,6-dibenzylidene-1,4-dimethyl-PDO and MeOH.[3)]

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