SYNTHESIS OF 3-(2-AMINO)BENZYLIDENE-2,5-PIPERAZINEDIONE AND ITS CONVERSION TO 1-AZANAPHTHALENONE AND SPIRO[INDOLINEPIPERAZINE]DIONE DERIVATIVES

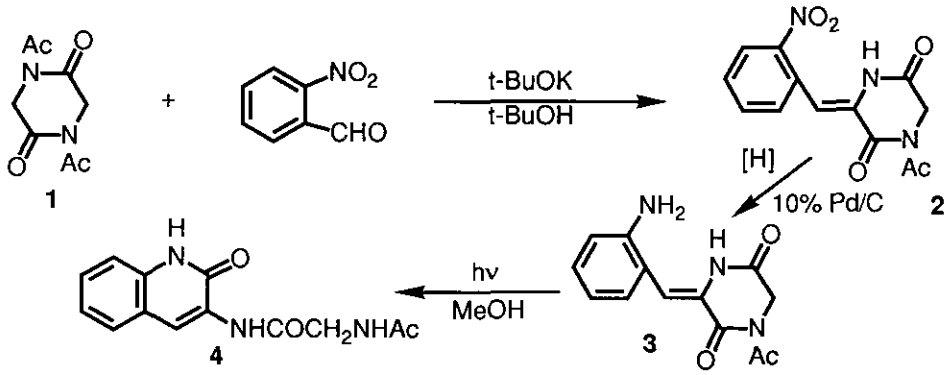
Yoshiaki Sato, Yoshiharu Nakajima, and Chung-gi Shin*

Laboratory of Organic Chemistry, Faculty of Technology, Kanagawa University, Kanagawa-ku, Yokohama 221, Japan

Abstract—Synthesis of 3-(2-amino)benzylidene-2,5-piperazinedione and its conversions by photolysis and by treatment with NBS gave 3-amino-1-azanaphthalen-2(H)-one and spiro[indoline-2(3H),2'-piperazine]-3',6'-dione derivatives, respectively.

In connection with the synthesis of aspirochlorin,[1] previously, we reported briefly that two kinds of intramolecular cyclization of 3-salicylidene-2,5-piperazinedione (2,5-piperazinedione=PDO), which was derived by the condensation of 1,4-diacetyl-PDO (**1**) with salicylaldehyde, gave 3-(acetylglycylamino)coumarin and spiro[benzofuran-2(3H),2'-piperazine]-3',6'-dione derivatives, respectively.[2] From these results, it is very interesting to explore the similar conversion of 3-arylidene-PDO derivatives possessing a protic functional group, such as $-NH_2$ at ortho position of phenyl group. In this paper, we wish to report on the synthesis of (Z)- and (E)-3-(2-amino)benzylidene-PDO derivatives and their conversions to 1-azanaphthalen-2-(H)-one and spiro[indoline-2(3H),2'-piperazine]-3',6'-dione derivatives. Since the direct condensation of **1** with 2-aminobenzaldehyde was found to be unsuccessful, after the condensation of **1** with 2-nitrobenzaldehyde in dimethylformamde (DMF) in the presence of t-BuOK by the usual method,[3] the

obtained (Z)-1-acetyl-3-(2-nitro)benzylidene-PDO (**2**) was subjected to the catalytic hydrogenation with 10% Pd/C in DMF to give (Z)-1-acetyl-3-(2-amino)benzylidene-PDO (**3**) in 60% yield. Subsequently, the irradiation of **3** with 500 W-high pressure mercury lamp[4] under stream of N_2 gas[2,5] gave 3-acetylglycylamino-1-azanaphthalen-2(H)-one (**4**) in 90% yield, as shown in Scheme 1. Consequently, as in the case of 3-sacylidene-PDO derivatives, the compound (**3**) was thought to be a desirable substrate for the synthesis of **4** and the other spiro-indoline derivatives.

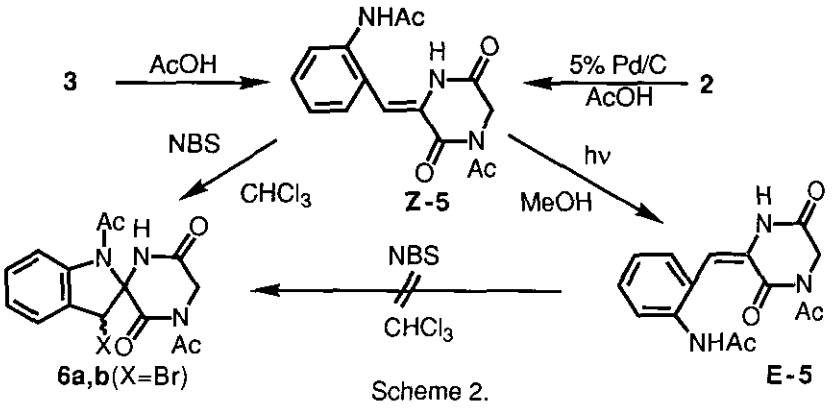


Scheme 1.

In order to confirm the structure and the configuration of **3**, the synthesis of the corresponding 2-acetylamino derivative and its geometric isomerization were carried out. The acetylation of NH_2 group of **3** with acetic acid gave (Z)-3-(2-acetylamino)benzylidene-PDO (**5**), which was in accord with the compound derived by the hydrogenation of **2** with 5% Pd/C in acetic acid. Although the subsequent photochemical transformation of **5** to the expected azanaphthalenone derivative was unsuccessful, the similar irradiation of **5** with 500 W-high pressure mercury lamp in MeOH gave the isomerized compound [(E)-**5**] in 61% yield.

The configuration of the two isomers of **5**, thus obtained, could be readily determined by the comparison of the chemical shifts of the olefin protons.

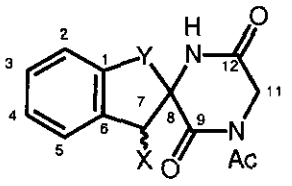
The signal of the olefin proton of (Z)-5 appeared at δ 6.94 as a singlet, while that of (E)-5 was observed at δ 6.46. Accordingly, the previous observations[6-8] that the olefin proton in the (E)-configuration of 3-alkylidene-PDO resonates at higher magnetic field than that in the (Z)-configuration support the structures of the two geometric isomers.



Scheme 2.

The compound [(Z)-5] was treated with N-bromosuccinimide (NBS) in $CHCl_3$ to give the expected spiro[1-acetyl-3-bromoindoline-2(3H),2'-(4'-acetyl)piperazine]-3',6'-dione (**6a,b**) as a mixture of diastereomers in 91% yield. The separation of the diastereomeric mixture was readily achieved by the chromatography on a silica gel column using a mixture of benzene and ethyl acetate as the eluent to give **6a** in 55% yield from the first fraction and **6b** in 36% yield from the second fraction. However, attempt on the similar conversion of (E)-5 with NBS was found to be unsuccessful (Scheme 2).

In order to confirm the spiro structure of **6**, the ^{13}C nmr spectral data of **6a** were investigated in detail and were compared with those of the main skeleton of aspirochlorin synthesized earlier by us.[5] As a result, as Table 1 shows, the ^{13}C nmr of **6a** was comparatively similar to that of spiro[benzofuran-2(3H),2'-piperazine]-3',6'-dione (**7**)[2] and all the signals could be reasonably assigned.



6a: X=Br, Y=NAc
7: X=Cl, Y=O

Table 1. Comparison of ^{13}C nmr data[a,b] of **6a** with **7**

1	138.2 s (155.4)[c]	7	54.9 d	(60.1)
2	125.2 d (110.8)	8	81.6 s	(91.7)
3	130.7 d (131.8)	9	165.8 t	(162.5)
4	113.6 d (123.3)	11	46.8 t	(46.1)
5	127.0 d (125.6)	12	166.0 s	(165.8)

a) δ Values are relative to tetramethylsilane in $CDCl_3$.
b) Letters of s, d, and t denote the result of half decoupling.
c) Numbers in parentheses denote the data of **7**.

In conclusion, the photochemical conversion and the intramolecular addition of 3-(2-substituent)benzylidene-PDO having 2-hydroxy or 2-amino group could be generalized.

EXPERIMENTAL

Melting points were determined with a Yamato micro melting point apparatus Mp-21 model and were uncorrected. The ir spectra were recorded with a Hitachi EPI-G2 grating spectrophotometer. The ^1H and ^{13}C nmr spectra were measured with JEOL FX 200 spectrometer, using tetramethylsilane as an internal standard.

(Z)-1-Acetyl-3-(2-nitro)benzylidene-2,5-piperazinedione (2): Into a solution of 1 (21.15 g, 106.8 mmol) and o-nitrobenzaldehyde (17.82 g, 117.5 mmol) in DMF (260 ml) was added 14.5 g (1.1 mol) of 0.5 M potassium t-butoxide, with stirring, at 0 °C for 1 h. After the addition, the resultant solution was stirred at room temperature for 12 h and neutralyzed with acetic acid. The resulting solution was then poured into ice water (1000 ml). A colorless crystalline substance deposited was collected and recrystallized from ethanol to give **2** as colorless needles. Yield, 28.9 g

(93%), mp 182-183 °C. Ir (KBr): 3200 (NH), 1720, 1690 (C=O), 1610 (C=C) cm^{-1}. ^1H Nmr (DMSO-d_6): δ 10.42 (br s, 1H, -NH-), 7.18 (s, 1H, -CH=), 4.36 (s, 2H, $-CH_2-$). Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83, N, 14.56. Found: C, 53.76; H, 3.75; N, 14.45.

(Z)-3-(2-Amino)benzylidene-2,5-piperazinedione (3): A solution of **2** (1.0 g, 3.5 mmol) in DMF (30 ml) was hydrogenated catalytically with 10% Pd/C (0.5 g) at room temperature for 3 h. After removing Pd/C, the reaction solution was concentrated under reduced pressure to give colorless crystals, which were recrystallized from ethanol to give **3** as colorless needles. Yield, 540 mg (60%), mp 168 °C (decomp.). Ir (KBr): 3340, 3230 (NH), 1690, 1560 (C=O), 1640 (C=C) cm^{-1}. ^1H Nmr (DMSO-d_6): δ 10.38 (br s, 1H, -NH-), 8.18 (br s, 2H, $-NH_2$), 4.46 (s, 1H, -CH=), 3.76 (s, 2H, $-CH_2-$). Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 59.89; H, 5.34; N, 15.98.

3-Acetylglycylamino-1-azanaphthalen-2(H)-one (4): A solution of **3** (0.5 g, 1.9 mmol) in methanol (50 ml) was irradiated with 500 W-high pressure mercury lamp under N_2 gas stream at room temperature for 5 h. The resultant solution was concentrated under reduced pressure to give residual crystals, which were subsequently recrystallized from methanol to give **4** as colorless needles. Yield, 450 mg (90%), mp 290 °C (decomp.). Ir (KBr): 3380, 3295 (NH), 1700 (C=O), 1640 (C=C) cm^{-1}. ^1H Nmr (CF_3COOH-D_2O): δ 8.95 (s, 1H, -CH=), 4.47 (s, 2H, $-CH_2-$), 2.41 (s, 3H, $-COCH_3$). Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.24; H, 4.82; N, 16.99.

(Z)-3-(2-Acetylamino)benzylidene-2,5-piperazinedione (5): A) From 3. A solution of **3** (0.1 g, 0.39 mmol) in acetic acid (10 ml) was stirred at

50 °C for 1.5 h. Subsequent concentration of the solution under reduced pressure gave the residual crystals, which were recrystallized from ethanol to give **5** as colorless needles. Yield, 115 mg (99%), mp 217-219 °C. Ir (KBr): 3350, 3240 (NH), 1720, 1680 (C=O), 1650 (C=C) cm^{-1}. ^1H Nmr (DMSO-d_6): δ 10.12, 9.40 (br s, 2H, -NH-), 6.94 (s, 1H, -CH=), 4.36 (s, 2H, $-CH_2-$). Anal. Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H. 5.02; N, 13.95. Found: C, 59.81; H, 5.05; N, 13.79.

B) From 2. A solution of **2** (620 mg, 2.0 mmol) in acetic acid (30 ml) was hydrogenated catalytically with 5% Pd/C (0.3 g) at room temperature for 3 h. After removing Pd/C, the reaction solution was concentrated under reduced pressure to give **5**. Yield, 480 mg (80%).

Isomerization of (Z)-5 to (E)-5: A solution of **(Z)-5** (500 mg, 1.7 mmol) in methanol (50 ml) was irradiated with 500 W-high pressure mercury lamp under N_2 gas stream at room temperature for 3 h. The resulting solution was concentrated under reduced pressure to give colorless crystals, which were recrystallized from ethanol to give **(E)-5** as colorless needles. Yield, 305 mg (61%), mp 180-181 °C. Ir (KBr): 3400, 3250 (NH), 1720, 1680 (C=O), 1630 (C=C) cm^{-1}. ^1H Nmr (DMSO-d_6): δ 10.24 (br s, 2H, -NH-), 4.30 (s, 2H, $-CH_2-$). Anal. Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.96. Found: C, 59.88; H, 5.03; N, 13.68.

Spiro[1-acetyl-3-bromoindoline-2(3H),2'-(4'-acetyl)piperazine]-3',6'-dione (6a,b): Into a suspension of **(Z)-5** (260 mg, 0.86 mmol) in $CHCl_3$ (30 ml) was added NBS (160 mg, 0.86 mmol), with stirring, at room temperature for 4 h. The reaction mixture was washed twice with water and the organic layer was dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the residual substance was chromatographed on a silica gel column using a mixture of benzene and ethyl acetate (5 : 1 v/v)

as the eluent to give two fractions. The first fraction was concentrated under reduced pressure to give **6a** as colorless powder. Yield, 180 mg (55%), mp 94-95 °C. Ir (KBr): 3240 (NH), 1720, 1690, 1660 (C=O) cm^{-1}. ^1H Nmr (DMSO-d_6): δ 7.96 (br s, 1H, -NH-), 6.04 (s, 1H, -CHBr-), 4.40 (ABq, J=18.0 Hz, 2H, -CH_2-). Anal. Calcd for $C_{15}H_{15}N_3O_4Br$: C, 47.79; H, 3.98; N, 11.05. Found: C, 47.58; H, 4.11; N, 11.35. The similar concentration of the second fraction gave **6b** as colorless powder. Yield, 120 mg (36%), mp 106-107 °C. Ir (KBr): 3230 (NH), 1780, 1695 (C=O) cm^{-1}. ^1H Nmr (DMSO-d_6): δ 8.24 (br s, 1H, -NH-), 5.57 (s, 1H, -CHBr-), 4.34 (ABq, J=18.0 Hz, 2H, -CH_2-). Anal. Calcd for $C_{15}H_{15}N_3O_4Br$: C, 47.79; H, 3.98; N, 11.05. Found: C, 47.61; H, 4.08; N, 10.91.

REFERENCES

1. D. H. Berg, R. P. Massing, M. M. Hoehn, L. D. Boeck, and R. L. Hamill, J. Antibiot., 1976, **26**, 394; K. Sakata, H. Masago, A. Sakurai, and N. Takahashi, Tetrahedron Lett., 1984, **23**, 2095; K. Sakata, M. Maruyama, J. Uzawa, A. Sakurai, H. S. M. Lu, and J. Clardy, Tetrahedron Lett., 1987, **28**, 5607.
2. C. Shin, Y. Nakajima, and Y. Sato, Chemistry Lett., **1984**, 1301.
3. C. Gallina and A. Liberatori, Tetrahedron, 1974, **30**, 667.
4. USHIO UM-453B-A.
5. C. Shin, Y. Nakajima, T. Haga, and Y. Sato, Bull. Chem. Soc. Jpn., 1986, **59**, 3917.
6. C. Shin, M. Hayakawa, K. Mikami, and J. Yoshimura, Tetrahedron Lett., **1977**, 866.
7. C. Shin, M. Hayakawa, T. Suzuki, A. Ohtsuka, and J. Yoshimura, Bull. Chem. Soc. Jpn., 1978, **51**, 550.
8. C. Shin, M. Hayakawa, H. Kato, K. Mikami, and J. Yoshimura, J. Chem. Soc., Perkin Trans. I, **1980**, 419.

Received, 30th October, 1991