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FACILE SYNTHESIS AND CONVERSION OF MAIN SKELETON OF ASPIROCHLORIN TO 3-AMINOCOUMARIN DERIVATIVES

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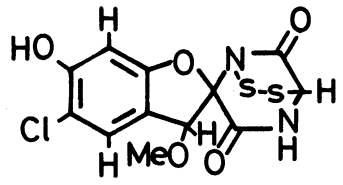
The condensation of 1,4-diacetyl-2,5-piperazinedione with salicylaldehyde gave 1-acetyl-(Z)-3-salicylidene-2,5-piperazinedione and 3-(N-acetylglycyl)aminocoumarin by ca. 1 : 1 ratio. The former was readily converted with t-BuOCl into spiro[3H-benzofuran-2,3'-(2',5'-dioxo)-piperazine] derivative which has a main skeleton of aspirochlorin.

Recently, the structure of aspirochlorin, isolated from the culture filtrate of Asperigillus flavus,[1] was revised from epidithiopiperazinobenzoxazinedione ring structure[2] to spiro[3H-benzofuran-2,3'-(2',5'-dioxo)-piperazine] structure, based on the ^{1}H- and ^{13}C-NMR spectral data and several chemical reactions.



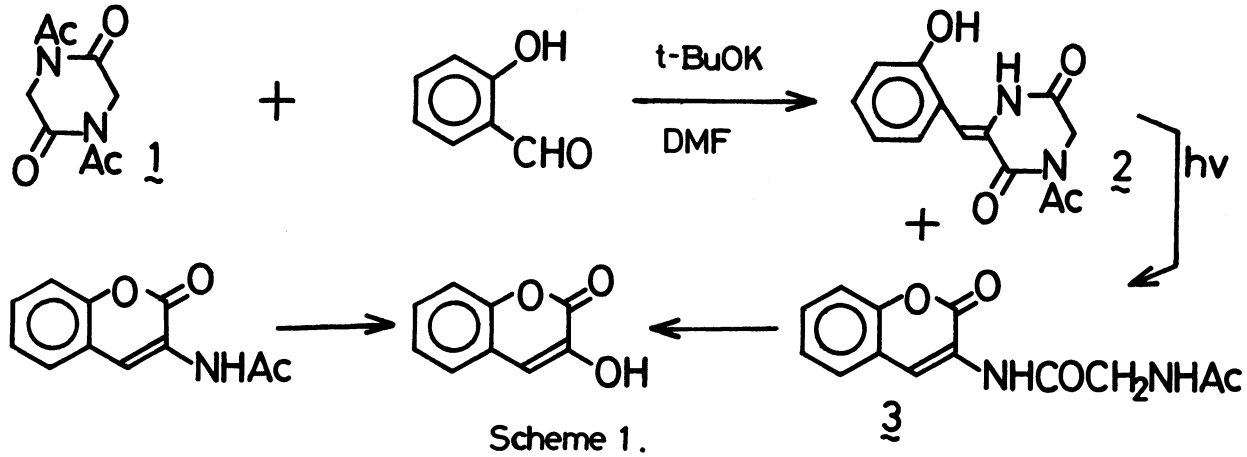
ASPIROCHLORIN

In connection with the synthetic study on bicyclomycin,[3] we reported the synthesis of a few spiro[oxolane-2,3'-(2',5'-dioxo)-piperazine] derivatives which are ring contracted products of bicyclomycin, by the reaction of 3-(3-hydroxypropylidene)-2,5-piperazinedione (2,5-piperazinedione=PDO) with N-bromosuccinimide (NBS) in MeOH.[4,5] Here, we wish to report the facile synthesis of the framework of didethioaspirochlorin and new synthesis of a 3-aminocoumarin derivative.

According to the method reported by Gallina,[6] 1,4-diacetyl-PDO (1; 200 mmol) was condensed with salicylaldehyde (200 mmol) in the presence of t-BuOK (200 mmol) in DMF (500 ml) to give (Z)-3-salicylidene-PDO [2; yield 53%, mp 200-201 °C. IR (KBr): 3070 (NH), 3380 (OH), 1705 (NHCO), 1630 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 10.56 (bs, OH), 10.00 (bs, NH), 7.03 (s, -CH=)] and another unknown product (3; $C_{13}H_{12}N_2O_4$, yield 43%, mp 212.5-213.5 °C). Subsequently, the compound 3 (23 mmol) was treated with 1 M HCl to give known 3-hydroxycoumarin (56%), which was completely consistent with the product derived by the reaction of 3-(N-acetyl)-

aminocoumarin with 1 M HCl.

From the above results and the spectral data [IR: 3315 (NH), 1690, 1535 (NHCO), 1620 (C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 9.64 (bs, NH), 8.33 (t, -CH_2N<u>H</u>-, J=5.5 Hz), 8.57 (s, -CH=), 4.06 (d, -CH_2-)], the structure of <u>3</u> was confirmed to be 3-(N-acetylglycyl)aminocoumarin.

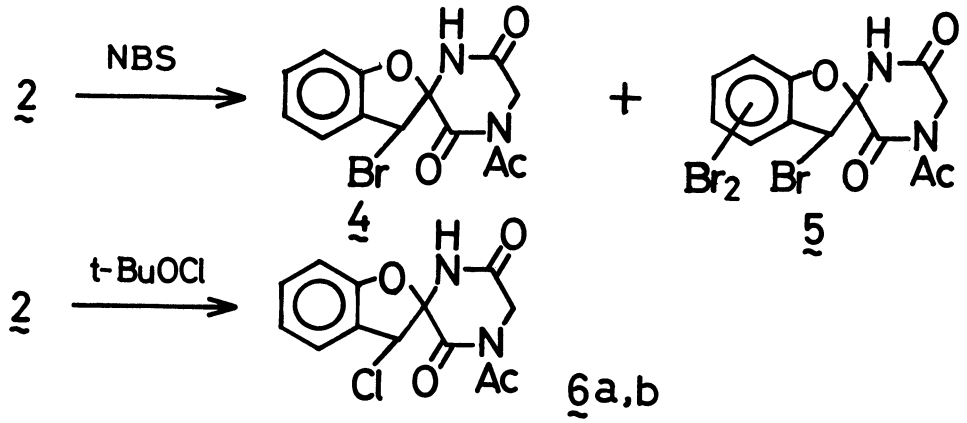


Scheme 1.

On the other hand, when a solution of (Z)-<u>2</u> (0.4 mmol) in MeOH (70 ml) was irradiated with a high pressure Hg lamp under stream of N_2 gas at room temperature,[7] the compound <u>3</u>, instead of the expected (E)-isomer of <u>2</u>, was obtained quantitatively. From the result, it was supposed that the condensation of <u>1</u> with salicylaldehyde proceeded to give a mixture of (Z)- and (E)-isomers and that the latter was immediately converted to give <u>3</u>, as shown in Scheme 1.

In order to synthesize the desired spiro-PDO derivative, (Z)-<u>2</u> (7.1 mmol) was reacted with NBS (14.2 mmol) in $CHCl_3$ (40 ml), according to the method reported previously,[5] to give two compounds. However, all attempts to separate them were unsuccessful. Judging from the result of the elemental analysis and the spectral data, it is assumed that the crystalline product obtained is composed of a 1 : 3 mixture of mono- and tribromo derivatives of spiro[3H-benzofuran-2,3'-(2',5'-dioxo)-piperazine] (<u>4</u> and <u>5</u>, yield 97%), as is shown in Scheme 2.

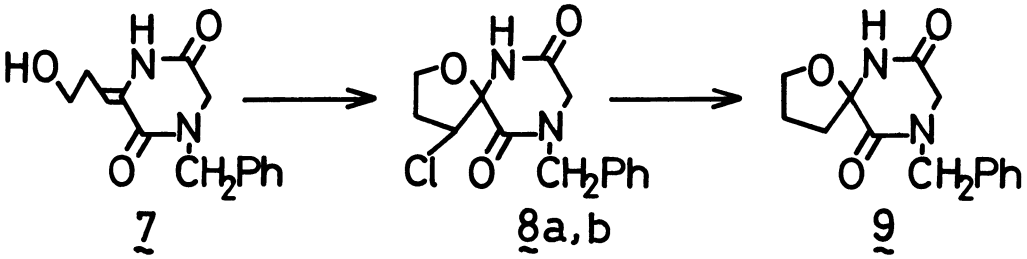
On the other hand, when (Z)-<u>2</u> (3.8 mmol) was treated with t-BuOCl (9.5 mmol) in $CHCl_3$ (30 ml) at room temperature for 30 min, spiro[3H-3-chlorobenzofuran-2,3'-(1'-acetyl-2',5'-dioxo)-piperazine] (<u>6</u>) was obtained as a mixture of two diastereomers (<u>6a</u>; yield 89%, mp 134-135 °C. IR: 3400 (NH), 1710 (CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 9.63 (bs, NH), 6.30 (s, -CHCl-), 4.37 (ABq, -CH_2-, J=18.0 Hz). <u>6b</u>;



Scheme 2.

yield 9%, mp 195-196 °C. IR: 3300 (NH), 1640 (CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 9.82 (bs, NH), 6.09 (s, -CHCl-), 4.36 (ABq, $-CH_2-$, J=18.0 Hz).

In order to ascertain the structure (6), 1-benzyl-3-(3-hydroxypropylidene)-PDO[5] (7; 1.9 mmol) was similarly reacted with t-BuOCl (2.7 mmol) to give spiro[3-chlorooxolane-2,3'-(1'-benzyl-2',5'-dioxo)-piperazine] (8) as a mixture of two diastereomers [8a; yield 83%, mp 128-129 °C. IR: 3200 (NH), 1695 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.75 (bs, NH), 5.00 (dd, -CHCl-, J=7.5 Hz, J=8.5 Hz). 8b; yield 10%, syrup. IR: 3250 (NH), 1680 (CO) cm^{-1}. ^{1}H-NMR: δ 8.40 (bs, NH), 4.31 (dd, -CHCl-, J=3.0 Hz, J=9.5 Hz)]. Subsequent hydrogenolysis of 8a with 10% Pd-C gave the authentic sample; spiro[oxolane-2,3'-(1'-benzyl-2',5'-dioxo)-piperazine] (9),[5] as illustrated in Scheme 3. Therefore, the formation of 8 was unambiguously proved here.



Scheme 3.

Furthermore, as Fig. 1 shows, not only the pattern of the ^{13}C-NMR spectrum of 6 was comparatively similar to that of aspirochlorin, but also all the signals were reasonably assigned. Particularly, the signal of tertiary bridgehead carbon (C-8) was found to be almost in accord with that (102.6 ppm) of aspirochlorin.

Interestingly, it was found that further treatment of 6a (2.6 mmol) with

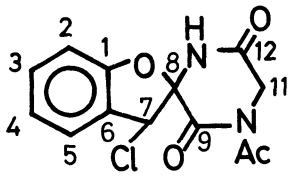
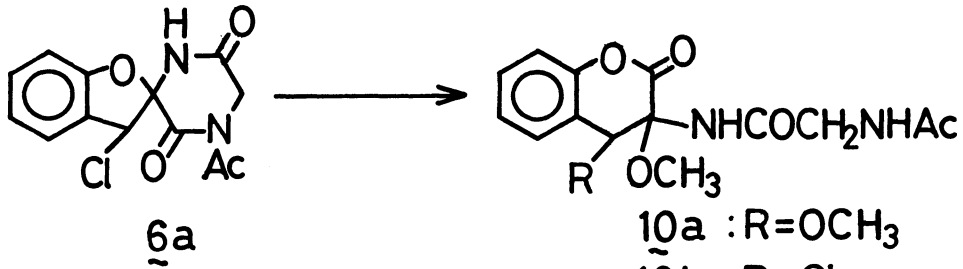


Table 1. ^{13}C-NMR data[a,b] of 6a

1	155.4 (s)	5	125.6 (d)	9	162.5 (s)
2	110.8 (d)	6	125.3 (s)	11	46.1 (t)
3	131.8 (d)	7	60.1 (d)	12	165.8 (s)
4	123.3 (d)	8	91.7 (s)		

a) δ Values are relative to tetramethylsilane in $CDCl_3$.
b) Letters in parentheses denote the result of half decoupling.

NaOMe (2.7 mmol) in MeOH (20 ml) gave 3-(N-acetylglycyl)amino-3,4-dimethoxy [10a; yield 52%, mp 163-164 °C. IR: 3390 (NH), 1660, 1505 (NHCO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 8.06 (bs, NH), 3.95 (d, $-CH_2-$, J=5.0 Hz), 4.82 (s, $-C\underline{H}(OCH_3)-$)]- and 4-chloro-3-methoxychroman [10b; yield 15%, mp 102-103 °C. IR: 3380 (NH), 1655, 1535 (NHCO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 9.10 (bs, NH), 8.21 (t, NH, J=7.0 Hz), 3.91 (d, $-CH_2-$, J=7.0 Hz), 6.09 (s, -CHCl-)]. On the other hand, similar treatment of 6a (3.4 mmol) with $ZnCO_3$ (8.0 mmol) gave 10a and 10b in 20 and 72% yields respectively.



6a

10a : R=OCH3
10b : R=Cl

Scheme 4.

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