Convenient Synthesis of 6-Substituted-2-chloro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinolines and *N*-acylated-3-chlorodibenz[*b,e*][1,4]oxazepin-11(5*H*)-ones

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Convenient synthesis of variously substituted 2-chloro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinolines at the 6-position and *N*-acylated-3-chlorodibenz[*b,e*][1,4]oxazepin-11(5*H*)-ones are reported. The former compounds were obtained in 65-93% yield by simply heating *N*-acyl-4-chloro-*N*-(2-hydroxyphenyl)-anthranilic acids in acetic anhydride for 4 hours, and the latter by heating sodium salt of *N*-acyl-4-chloro-*N*-(2-hydroxyphenyl)anthranilic acids with acetic anhydride.

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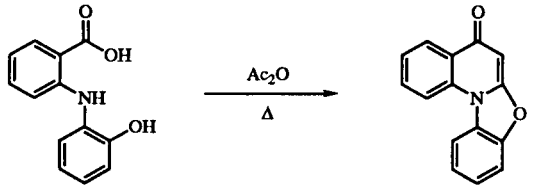
In 1974, Kim *et al.* reported that treatment of *N*-(2-hydroxyphenyl)anthranilic acid with refluxing acetic anhydride affords 5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]-quinoline in good yield [1]. This tandem double ring closure reaction has served as a simple and convenient method for the preparation of benzoxazoloquinolones which are otherwise difficult to prepare [1]. In connection with our effort to synthesize potential quinolone antibacterial agents, we have recently reexamined the reaction and have expanded its scope [2,3]. Thus, a simple modification of the reaction procedure has made the preparation of benzoxazoloquinolones having an ethoxycarbonyl substituent at the 6-position possible [2,3]. This paper reports synthesis of variously substituted benzoxazoloquinolones at the 6-position by the modified method. During the course of this study we have discovered that, interestingly, sodium salt of *N*-acyl-4-chloro-*N*-(2-hydroxyphenyl)anthranilic acids take an entirely different cyclization path when they were treated with acetic anhydride under the similar conditions to give *N*-acylated-3-chlorodibenz[*b,e*][1,4]oxazepin-11(5*H*)-ones. This lactone formation reaction is also described.



The starting material, 4-chloro-*N*-(2-hydroxyphenyl)-anthranilic acid (**1**) for the present study was synthesized according to literature methods [1,2] which involves the condensation of potassium 2,4-dichlorobenzoate with 2-aminophenol under conditions of the Ullmann condensation. Treatment of **1** with various acyl chlorides in the presence of 3 molar equivalent amount of imidazole afforded exclusively the *N*- acylated products **2** in 70~85% yield (Table 1). The excess amount of imidazole appears to be essential for the reaction to proceed in satisfactory yield. We have previously demonstrated that *N*-carbethoxyacetyl-4-chloro-*N*-(2-hydroxyphenyl)anthranilic acid (**2c**) was produced, *via* $O \rightarrow N$ acyl migration, from the anhydride intermediate that was formed initially from the reaction of the carboxylate group of **1** with carbethoxyacetyl chloride [2]. Treatment of **2** with hot acetic anhydride for 4 hours afforded 6-substituted-2-chloro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinolines **3** in yields ranging from 65% to 93% (Table 2).

Scheme 1

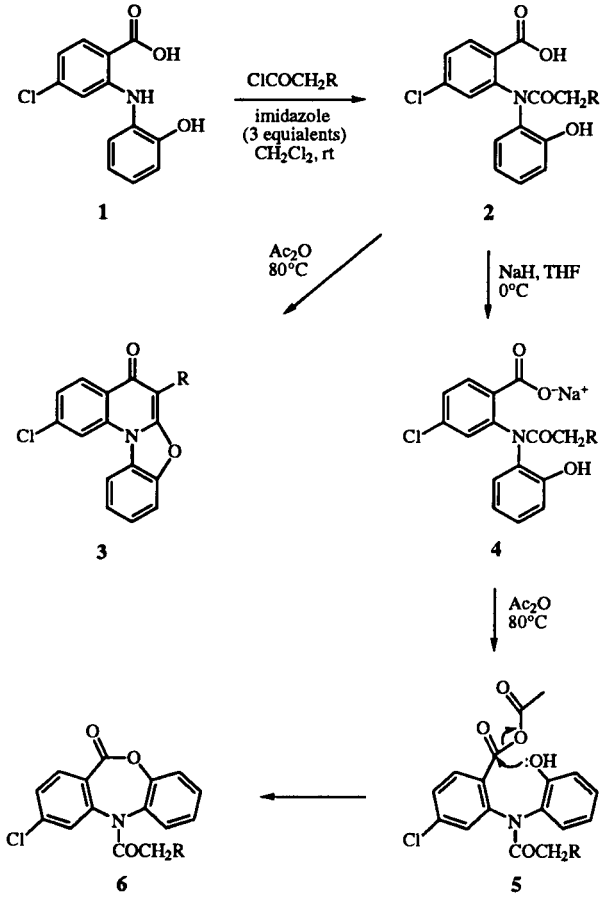
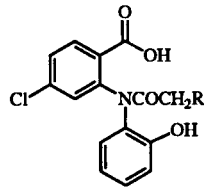


Table 1



Compound No.	R	Yield (%)	Mp (°C)	Molecular Formula	Calcd./Found Analysis (%) C	H	N
2a	Me	78	175-177	$C_{16}H_{14}ClNO_4$	60.10	4.41	4.38
					59.80	4.40	4.22
2b	Et	80	174-176	$C_{17}H_{16}ClNO_4$	61.18	4.83	4.20
					61.19	4.63	4.09
2c	CO_2Et	72	159.5-162.5	$C_{18}H_{16}ClNO_6$	57.22	4.27	3.71
					57.29	4.27	3.70
2d	Ph	81	175-178	$C_{21}H_{16}ClNO_4$	66.06	4.22	3.67
					66.07	4.54	3.43
2e	Bn	85	163-164	$C_{22}H_{18}ClNO_4$	66.75	4.58	3.54
					66.87	4.54	3.38
2f	OPh	75	160-162	$C_{21}H_{16}ClNO_5 \cdot H_2O$	60.65	4.36	3.37
					60.39	4.35	3.05
2g	OMe	70	179-182	$C_{16}H_{14}ClNO_5$	57.24	4.20	4.17
					57.44	4.03	3.91
2h	OC_6H_{11}	70	180-181.5	$C_{21}H_{22}ClNO_5$	62.38	5.50	3.38
					62.45	5.49	3.47

While **2** afforded benzoxazoloquinolones **3** by the treatment with hot acetic anhydride, sodium salts **4** of **2** produced *N*-acyl-3-chlorodibenz[*b,e*][1,4]oxazepin-11(5*H*)-ones **6** upon treatment with acetic anhydride under similar conditions (Table 3). These compounds showed the characteristic lactone carbonyl absorption in their ir spectra. In addition, one of *N*-acyl-3-chlorodibenz[*b,e*][1,4]oxazepin-11(5*H*)-ones thus obtained, *i.e.*, **6b** was identical with an authentic sample prepared by the literature method [2].

Presently, we are not certain why the sodium salts take an alternative reaction path to generate **6** under similar conditions. However, it is not unreasonable to speculate that while in the case of **2**, the acetylation of the phenolic hydroxyl precedes or parallels the acetylation of the carboxyl group to form the mixed anhydride upon the treatment with acetic anhydride [1,2], the sodium salts **4** form the mixed anhydride first under the reaction conditions, which then undergoes an intramolecular cyclization reaction with the phenolic hydroxyl to yield lactones **6**. Apparently, the carboxylate is a better nucleophile than the phenolic hydroxyl and carboxylic acid in the reaction with acetic anhydride.

In conclusion, we have developed a convenient synthetic method for the preparations of 6-substituted-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinolones and *N*-acyl-3-chlorodienz[*b,e*][1,4]oxazepin-11(5*H*)-ones, which involves simple heating of *N*-acyl-4-chloro-*N*-(2-hydroxyphenyl)anthranilic acids **2** and their sodium salts **4** with acetic anhydride, respectively.

EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. The nmr spectra were recorded on a Bruker FT-*N*MR (300 MHz) in deuteriochloroform or dimethyl sulfoxide-d_6 solution. Chemical shifts are reported in ppm (δ) values relative to tetramethylsilane as internal reference. Infrared (ir) absorption spectra were obtained in a potassium bromide pellet using a Perkin-Elmer Model 843 spectrometer. Microanalyses were performed by the Korea Basic Science Center on a Carlo Erba elemental analyzer type CE 1108.

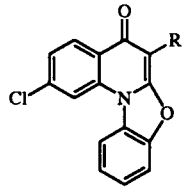
4-Chloro-*N*-(2-hydroxyphenyl)anthranilic Acid (**1**).

Following the literature method [2], **1** was obtained from potassium 2,4-dichlorobenzoate (22 g) and 2-aminophenol (2.5 equivelents) under Ullmann conditions in 33% yield, mp 203-205°, lit mp 203-205° [2].

N-Propionyl-4-chloro-*N*-(2-hydroxyphenyl)anthranilic Acid (**2a**).

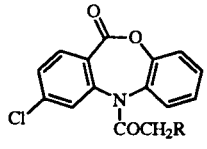
To a suspension of **1** (530 mg, 2 mmoles) and imidazole (410 mg, 6 mmoles) in dichloromethane (30 ml) was added propionyl chloride (204 mg, 0.19 ml, 2.2 mmoles) and the resulting solution was stirred at ambient temperature for 4 hours, and then refluxed for 2 hours. The reaction mixture diluted with dichloromethane (50 ml) was washed with 3*N* hydrochloric acid (30 ml x 2) and extracted with 0.1 *N* sodium hydroxide (10 ml).

Table 2



Compound No.	R	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
3a	Me	93	223-226	$C_{16}H_{10}ClNO_2$	67.73	3 55	4.94
					67.61	3.50	4.88
3b	Et	90	229-231.5	$C_{17}H_{14}ClNO_2$	68.57	4.06	4.70
					68.20	4.09	4.65
3c	CO_2Et	92	220.2-221.5	$C_{18}H_{16}ClNO_4$	63.26	3.54	4.10
					63.27	3.24	3.72
3d	Ph	90	228-230	$C_{21}H_{12}ClNO_2$	72.94	3.50	4.05
					72.92	3.54	3.87
3e	Bn	89	217-220	$C_{22}H_{14}ClNO_2$	73.44	3.92	3.89
					73.38	3.93	4.02
3f	OMe	90	257-258	$C_{16}H_{10}ClNO_3$	64.12	3.36	4.67
					63.80	2.96	4.29
3g	OC_6H_{11}	65	190.5-191.5	$C_{21}H_{18}ClNO_3$	68.63	4.92	3.75
					68.57	4.93	3.81

Table 3



Compound No.	R	Yield (%)	Mp (C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
6a	Me	78	153-154	$C_{16}H_{12}ClNO_3$	63.69	4.01	4.64
					63.61	3.99	4.52
6b	CO_2Et	85	115-117	$C_{18}H_{14}ClNO_5$	60.09	3.92	3.89
					60.12	3.91	3.92
6c	Ph	79	179-180	$C_{21}H_{14}ClNO_3$	69.33	3.88	3.85
					69.33	3.95	3.68
6d	Bn	78	145-146.5	$C_{22}H_{16}ClNO_3$	69.94	4.27	3.71
					70.05	4.33	3.52
6e	OPh	90	210-212	$C_{21}H_{14}ClNO_4$	66.41	3.72	3.69
					66.36	3.42	3.58

The aqueous layer was acidified to ~*p*H 2 with 3*N* hydrochloric acid, whereby a precipitation occurred. The collected precipitate was recrystallized from ethyl acetate-hexane to give **2a** (500 mg, 78%) as white crystals, mp 175-177°; ir (potassium bromide): 3600-2500 (OH), 1696, 1664 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.00 (3H, t), 2.15 (2H, q), 6.94 (1H, t), 7.11 (1H, d), 7.26-7.36 (2H, m), 7.46 (1H, dd), 7.54 (1H, d), 7.87 (1H, d), 10.31 (1H, s); ms: FAB m/z 342 (M^+ + Na), 320 (MH^+).

Anal. Calcd. for $C_{16}H_{14}ClNO_4$: C, 60.10; H, 4.41; N, 4.38. Found: C, 59.80; H, 4.40; N, 4.22.

Compounds **2b-h** were prepared similarly (Table 1).

6-Methyl-2-chloro-5,12-dihydro-5-oxobenzoxazolo[3,2-*a*]quinolines (**3a**).

A solution of **2a** (0.8 g, 2.5 mmoles) in acetic anhydride (10 ml) was stirred at 80° for 4 hours. The reaction mixture was poured into an ice-water mixture. A precipitate that was separated was filtered and recrystallized from ethanol to afford **3a** as a white crystalline solid, mp 223-226°; ir (potassium bromide): 1664 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.29 (3H, s), 7.37-7.55 (4H, m), 7.93 (1H, q), 8.13 (1H, d), 8.53 (1H, d); ms: EI m/z 297 (M^+).

Anal. Calcd. for $C_{16}H_{10}ClNO_2$: C, 67.73; H, 3.55; N, 4.94. Found: C, 67.61; H, 3.50; N, 4.88.

Similarly were prepared **3b-g** (Table 2).

N-Propionyl-3-chlorodibenz[*b,e*][1,4]oxazepin-11-one (**6a**).

To a solution of **2a** (0.8 g, 2.5 mmoles) in THF (20 ml) was slowly added 60% sodium hydride (100 mg, 2.5 mmoles) at 0° and stirred for 1/2 hour. The reaction mixture was evaporated to dryness, the residue was dissolved in acetic anhydride (10 ml), and the resulting solution was stirred at 60° for 4 hours. The reaction mixture was then poured into an ice-water (50 ml) mixture, and a precipitate was collected on a filter. The filtered residue was recrystallized from ethyl acetate-hexane to give **6a** as white crystals, mp 153-154°; ir (potassium bromide): 1742, 1682 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.16 (3H, t), 2.5-2.6 (2H, m), 7.20-7.60 (6H, m), 7.89 (1H, d).

Anal. Calcd. for $C_{16}H_{10}ClNO_3$: C, 63.69; H, 4.01; N, 4.64. Found: C, 63.61; H, 3.99; N, 4.52.

Compounds **6b-e** were similarly prepared (Table 3).

Acknowledgments.

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