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Synthesis of (*1H*)-3,4-Dihydropyrrolo[2,1-c][1,4]oxazin-1-one Derivatives

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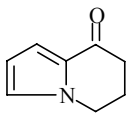
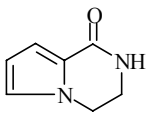
Abstract: In search of new anti-inflammatory and analgesic agents, (*1H*)-3,4-dihydro- pyrrolo [2,1-c][1,4]oxazin-1-one (**3**) and its acyl derivatives were designed and prepared. Compound **3** was prepared by treatment of methyl 1-(2-bromoethyl) pyrrole-2-carboxylate with silver oxide and its derivatives were obtained by Friedel-Craftes reaction. Nine of 6-acyl derivatives of compound **3** were prepared.

Keywords: (*1H*)-3,4-Dihydropyrrolo[2,1-c][1,4]oxazin-1-one, synthesis.

It has been found that some acyl derivatives of 1,2,3,4-tetrahydro-1-indolizin-1-one **1** and (*1H)*-3,4-dihydropyrrolo[1,2-a]pyrazin-1-one **2** show remarkable anti-inflammatory and analgesic activities[1,2]. The interest in extending the study of structure-activity relationships and search of new potent anti-inflammatory and analgesic agents led us to design and synthesize (*1H)*-3,4-dihydropyrrolo[2,1-c][1,4]oxazin-1-one **3** derivatives.



1



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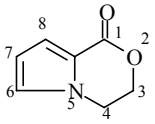

3

A few examples of the pyrrolo[2,1-c][1,4]oxazine ring-system have been reported, but the synthesis of (*1H*)-3,4-dihydropyrrolo[2,1-c][1,4]oxazin-1-one **3** has not been found in literature. Irwin has reported the synthesis of some 3-phenyl derivatives of the compound **3** by the cyclization of 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxilic acid, which was prepared from potassium methyl pyrrole-2-carboxylate and styrene oxide (**Scheme 1**)[3].

With this synthetic scheme, started from ethylene oxide instead of styrene oxide, Irwin was not successful in the synthesis of compound **3** itself [3].

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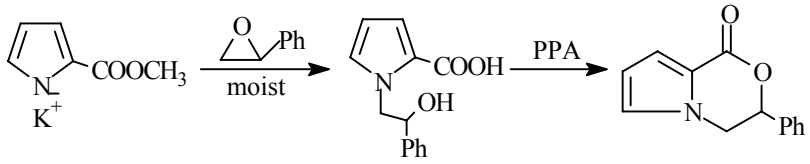
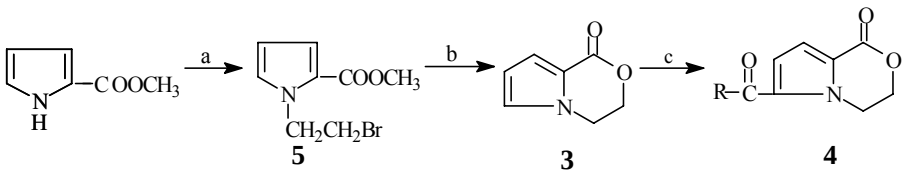
Scheme 1



We designed a new synthetic scheme, and compound **3** was successfully synthesized. Methyl pyrrole-2-carboxylate was prepared by Bailey's procedure[4]. When it reacted with excess 1,2-dibromoethane, methyl 1-(2-bromoethyl)pyrrole-2-carboxylate **5** was obtained with high yield. Treated compound **5** with silver oxide in 25% methanol solution, compound **3** was successfully obtained (**Scheme 2**). Friedel-Craftes acylation of **3** with acid chlorides in 1,2-dichloroethane afforded 6-acyl-3,4-dihydropyrrolo- [2,1-c][1,4]oxazin-1-ones **4**.

Scheme 2



a: $BrCH_2CH_2Br$, $(n\text{-}Bu)_4N^+Br^-$/ NaOH b: Ag_2O c: RCOCl

Experimental

Melting points were determined with capillary method, and the thermometer was uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker ARX-300 spectrometer. MS was measured with GCMSQP-1000 instrument.

Methyl 1-(2-bromoethyl)pyrrole-2-carboxylate ***5***

A mixture of 3.3 g (26.4 mmol) methyl pyrrole-2-carboxylate, 3 mL 50% aqueous sodium hydroxide and 0.2 g tetrabutylammonium bromide in 20 mL 1,2-dibromoethane was stirred at room temperature for 5 h. The reaction mixture was washed with water (15 mL × 3), and the organic layer was dried over $MgSO_4$. After recovering the excess 1,2-dibromoethane by vacuum distillation, crude product was obtained as a sticky oil. It was purified by column chromatography on silica-gel; eluted with petroleum ether/ethyl acetate (6:1) 5.8 g methyl 1-(2-bromoethyl)pyrrole-2-carboxylate **5** was obtained as an oil, bp 122-124°C/10 mm (lit.[5] 131-133°C /15 mm), yield 94%.

(1H)-3,4-Dihydropyrrolo[2,1-c][1,4]oxazin-1-one 3

A mixture of 2.0 g (8.6 mmol) compound **5** and 1.0 g (4.3 mmol) silver oxide in 25 mL 25% methanol solution was stirred at 60~70°C for 6 h. The mixture was cooled and filtered. The filtrate was extracted with dichloromethane (20 mL × 3). The combined extracts were washed with water, dried over Na_2SO_4. After removing the solvent on the rotary evaporator, a pale-yellow solid was afforded. The crude product was re-crystallized from petroleum ether/ethyl acetate (1:3). 0.7 g of compound **3** was obtained as a white needle crystal, mp 62~63°C, yield 60%. MS*(m/z)* : 137(M^+, 100%), 107, 79, 52, 39, 27. ^{1}H-NMR (δ, ppm, $CDCl_3$): 4.21 (t, 2H, J=5.25Hz, H-4), 4.61 (t, 2H, J=5.25Hz, H-3), 6.30 (dd, 1H, $J_{6,7}$=2.53 Hz, $J_{7,8}$=3.89 Hz, H-7), 6.89 (m, 1H, H-6), 7.11 (dd, 1H, $J_{6,8}$=1.32 Hz, $J_{7,8}$=3.93 Hz, H-8). ^{13}C-NMR (δ, ppm, $CDCl_3$): 43.1, 66.0 , 110.7 , 117.5 , 119.4 , 124.7 , 158.6.

General procedure for the synthesis of compound 4

A mixture of 1.0 g (7.3 mmol) of compound **3** and 3.7 g (28 mmol) anhydrous aluminum chloride in 25 mL 1,2-dichloroethane was stirred at 0°C for 30 min. And then a solution 9.5 mmol acid chloride in 10 mL 1,2-dichloroethane was added dropwise at 0~5°C. The reaction mixture was stirred at 0~5°C for 6 h, and then at room temperature for 2 h. The mixture was poured into 30 g ice-water containing 5 mL concentrated hydrochloric acid. The organic layer was separated, and the water layer was extracted with 1,2-dichloroethane (15 mL × 2). Combined the organic phases, dried over Na_2SO_4, and the solvent was removed by vacuum distillation. The solid residue was crystallized from ethyl acetate or petroleum ether/ethyl acetate, the 6-acyl-(*1H*)-3,4-dihydropyrrolo-[2,1-c][1,4]oxazin-1-one **4** was obtained. All the compounds **4** (**4a-4i**) are white crystals. The structures and some physical data are presented in the **Table**.

Pharmacological tests

The anti-inflammatory activities were evaluated by the xylene-induced ear edema on mice, and the analgesic activities were evaluated by acetic acid-induced writhing method. The primary results showed some of compounds **4** had some anti-inflammatory and/or analgesic activities, but they were all lower than the activities of ibuprofen.

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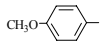
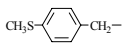
Table The structure and physical data of compound **4**

Compd.	R	mp (°C)	^{1}H-NMR(δ, ppm, $CDCl_3$)
4a		172-173	4.30 (t, J=5.3Hz, 2H), 4.68 (t, J=5.3Hz, 2H), 7.46-7.56 (m, 5H), 7.83 -7.85 (m, 2H).
4b		176-178	2.44 (s, 3H), 4.30 (t, J=5.3Hz, 2H), 4.66 (t, J=5.3Hz, 2H), 7.30 (m, 2H), 7.48-7.52 (m, 2H), 7.74-7.77 (m, 2H).
4c		165-168	4.31 (t, J=5.3Hz), 4.68 (t, J=5.3Hz, 2H), 7.44-7.53 (m, 4H), 7.80-7.82 (m, 2H).
4d		146-149	3.90 (s, 3H), 4.30 (t, J=5.3Hz, 2H), 4.67 (t, J=5.3Hz, 2H), 6.96- 6.99 (m, 2H), 7.50-7.55 (m, 2H), 7.81 -7.90 (m, 2H).
4e		136-138	4.28 (t, J=5.3Hz, 2H), 4.66 (t, 2H), 7.30 (m, 1H), 7.35 (m, 2H), 7.43 (m, 1H), 7.49 (m, 1H).
4f		152-154	4.30 (t, J=5.3Hz, 2H), 4.66 (t, J=5.3Hz, 2H), 7.32-7.48 (m, 6H).
4g		174-176	4.06 (s, 2H), 4.23 (t, J=5.3Hz, 2H), 4.62 (t, J=5.3Hz, 2H), 7.28-7.30 (m, 5H), 7.46 (m,1H), 7.50 (m, 1H).
4h		180-182	4.32 (t, J=5.3Hz, 2H), 4.68 (t, J=5.3Hz, 2H), 7.14-7.20 (m, 2H), 7.47 (m, 1H), 7.53 (m, 1H), 7.87-7.91 (m. 2H).
4i		156-158	2.46 (s, 3H), 4.01 (s, 2H), 4.23 (t, J=5.3Hz, 2H), 4.62 (t, J=5.3Hz, 2H), 7.20 (m, 4H), 7.45 (m, 1H), 7.50 (m, 1H).

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