## NOTES

## REVISED STRUCTURE FOR ARGLECIN

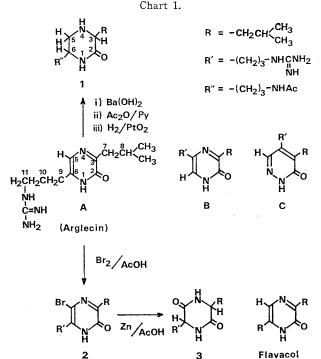
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Arglecin<sup>1)</sup> is a metabolite produced by several *Streptomyces* and found to possess antiarrhythmic properties. We wish in this report to revise the structure of this compound and propose it to be 6-(3-guanidinopropyl)-3-isobuthyl-2(1H)-pyrazinone (A). Dr. J.C. MACDONALD suggested, in his private communication to us, a 2(1H)-pyrazinone structure for arglecin mainly on the basis of the similarity of UV spectrum of arglecin



\* The signals were overlapped with H-9 signals.

to those of flavacol<sup>2</sup>) and other related compounds<sup>3</sup>.

When the NMR spectrum (100 MHz) of arglecin dihydrochloride was examined immediately after dissolution in deuterium oxide, the presence of 2-proton doublet (J 7Hz) at  $\delta$  2.84 (H-7,7'\*) was observed, denying the previously reported structure. Other signals can be interpreted by either A or the previously reported structure. The structure A has further been supported by the findings of a long-range coupling (J < 1Hz)as well as nuclear Overhauser effect between H-5 and H-9, that is, irradiation at  $\delta$  2.87 (H-9) caused the signal at  $\delta$  7.5 (H-5) to change into a sharpened singlet and an increase of 28 % of the area; irradiation at  $\delta$  7.5, on the contrary, caused the triplet of H-9 to change into a sharp triplet.

As for the strong peak of m/e 209 (M<sup>+</sup>-42) in the mass spectrum of arglecin, we had interpreted<sup>1)</sup> it by McLAFFERTY rearrangement, however, M<sup>+</sup>-42 peak is also observed in the mass spectra of flavacol and related compounds, although reasonable inter-

pretation of this peak is not yet known. Therefore, the peak can be interpreted by structure **A**.

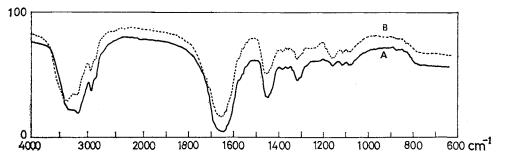
The pKa values of arglecin were measured in 66 % DMF instead of in water<sup>1)</sup> and three values (4.6, 10.1 and >13) were obtained, suggesting the presence of one weak base, one phenolic group and one strong base. In the case of flavacol we obtained two similar pKa values (4.7 and 10.8) in the same condition.

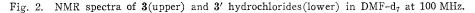
The above-mentioned results suggested the structure A, B or C for arglecin.

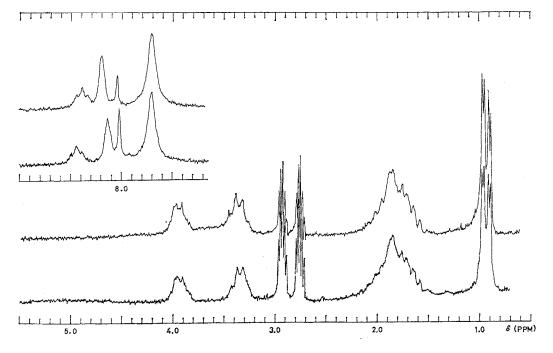
The NMR spectrum of 1 in DMSOd<sub>6</sub> showed the methine proton at  $\delta$ 3.62 coupled to the imino proton at  $\delta$  8.31, excluding the structure C, because an anticipated hexahydropyridazinone structure from C does not conform to the above result.

The structure  $\mathbf{B}$  was excluded by the fact that arglecin is convertible into diketopiperazine (3) by bromination followed by treatment with zinc dust and acetic acid<sup>4</sup>): A solution of arglecin (430 mg) in 80 % aqueous acetic acid (4.3 ml) was treated with a solution of bromine (370 mg) in acetic acid (2.8 ml) at room temperature for 1 hour to give a monobromo derivative (2), which was diacetyl-positive. Purification by cellulose column chromatography and recrystallization from ethyl acetate-ethanol gave a monohydrobromide of 2 (210 mg), mp 192~193°C; Anal. Found: C 35.31, H 5.01, N 16.77, Br 38.81 %. Calcd. for C<sub>12</sub>H<sub>20</sub>N<sub>5</sub>OBr · HBr : C 35.05, H 5.15, N 17.03, Br 38.87 %. On TLC with "Avicel" and n-butanol - ethanol - water (4:1:2) (Solvent I), 2 showed a single spot of Rf 0.61 (arglecin Rf 0.54). UV spectrum :  $\lambda_{\max}^{H_{\epsilon}O}(\epsilon)$  333 m $\mu$ (15,400), 236 mµ (15,700); NMR spectrum (D<sub>2</sub>O, 60 MHz):  $\delta$  1.01 [6H, d, J ~6Hz, (CH<sub>3</sub>)<sub>2</sub>-CH], 1.9~2.4 (3H, m, H-8 and CH<sub>2</sub>-10), 2.70 (2H, d, J 8Hz, CH<sub>2</sub>-7), 2.91 (2H, t, J 8Hz, CH<sub>2</sub>-9), 3.41 (2H, t, J ~7Hz, CH<sub>2</sub>-The signal of H-5 was no longer 11). discerned, supporting that only the H-5 proton was substituted for a bromine. The product 2 (210 mg) was refluxed with zinc dust (500 mg) in 80 % aqueous acetic acid (10 ml) with stirring for 1 hour. The crude product, which showed virtually a diacetylpositive single spot (Rf 0.4) on TLC with cellulose "Av<sub>c</sub>cel" and Solvent I, was chro-

Fig. 1. Infrared spectra of 3 hydrochloride(A) and 3' hydrochloride(B) in KBr disk.



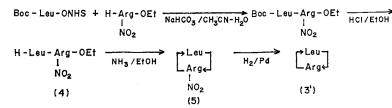




none (A).

matographed on a column of Amberlite CG-50 resin (H-form, 10 ml,  $1.0 \times 14$  cm) with water and then with 0.1 N hydrochloric acid to give a monohydrochloride-monohydrate (120 mg) of **3**, which was recrystallized from ethanol-ether; mp 160~162°C (dec.),  $[\alpha]_{1}^{14}$ 0° (c 1.0, ethanol). Anal. Found: C 44.63, H 7.99, N 20.89, Cl 10.74 %. Calcd. for C<sub>12</sub>H<sub>28</sub>N<sub>5</sub>O<sub>2</sub>·HCl·H<sub>2</sub>O: C 44.51, H 8.09, N 21.63, Cl 10.95 %.

Hydrolysis of **3** with 48 % hydrobromic acid overnight in a sealed tube at 110°C gave leucine and arginine. This result suggested that **3** is 2,5-diketopiperazine composed of leucine and arginine. Then, 3s:6s-6-(3guanidinopropyl)-3-isobutyl-2, 5-diketopiperazine (**3**') was synthesized from nitro-Larginine ethyl ester monohydrochloride<sup>5</sup> and *t*-butyloxycarbonyl-L-leucine N-hydroxysuccinimide ester<sup>6</sup>) by a sequence of reactions as shown below.



The intermediary **4** [monohydrochloride: mp 178~180°C,  $[\alpha]_D^{25}$  +10° (*c* 1.0, ethanol)] was treated with ethanolic ammonia to give 3s: 6s-3-isobutyl-6-(3-nitroguanidinopropyl)-2, 5-diketopiperazine [**5**; mp 228~230°C,  $[\alpha]_D^{16}$ -37° (*c* 1.0, 50% acetic acid)], which was hydrogenated with palladium and hydrogen to give an optically active isomer (**3**') of 2,5diketopiperazine monohydrochloride-monohydrate, mp 165~172°C (dec.),  $[\alpha]_D^{14}$  -15°

## Acknowledgement

(3-guanidinopropyl)-3-isobutyl-2(1H)-pyrazi-

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