

NOTES

REVISED STRUCTURE FOR ARGLEGIN

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Arglecin¹⁾ 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-guanidino-propyl)-3-isobutyl-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

to those of flavacol²⁾ and other related compounds³⁾.

When the NMR spectrum (100 MHz) of arglecin dihydrochloride was examined immediately after dissolution in deuterium oxide, the presence of 2-proton doublet (J 7 Hz) at δ 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 <1 Hz) as well as nuclear OVERHAUSER effect between H-5 and H-9, that is, irradiation at δ 2.87 (H-9) caused the signal at δ 7.5 (H-5) to change into a sharpened singlet and an increase of 28 % of the area; irradiation at δ 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 ($M^+ - 42$) in the mass spectrum of arglecin, we had interpreted¹⁾ it by McLAFFERTY rearrangement, however, $M^+ - 42$ peak is also observed in the mass spectra of flavacol and related compounds, although reasonable interpretation of this peak is not yet known. Therefore, the peak can be interpreted by structure **A**.

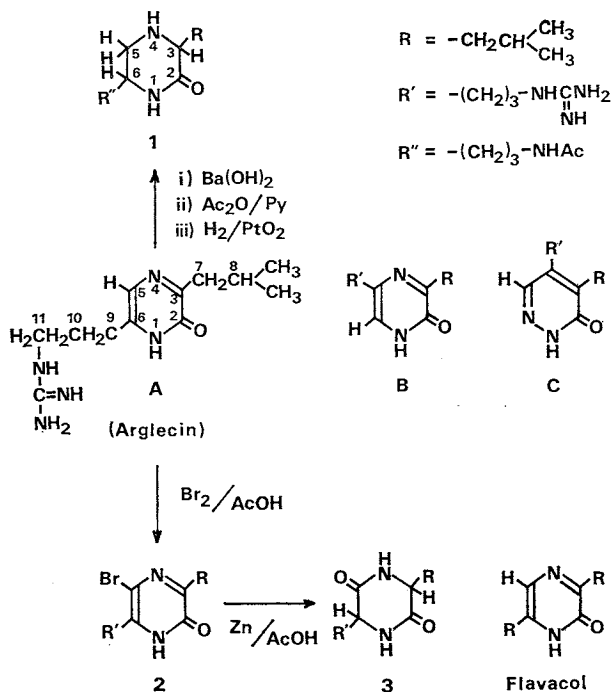
The pKa values of arglecin were measured in 66 % DMF instead of in water¹⁾ and three values (4.6, 10.1 and >13) were obtained, suggesting the presence of one weak base, one phenolic group and one strong base. In the case of flavacol we obtained two similar pKa values (4.7 and 10.8) in the same condition.

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

The NMR spectrum of **1** in DMSO-d₆ showed the methine proton at δ 3.62 coupled to the imino proton at δ 8.31, excluding the structure **C**, because an anticipated hexahydropyridazinone structure from **C** does not conform to the above result.

The structure **B** was excluded by the fact that arglecin is convertible

Chart 1.



* The signals were overlapped with H-9 signals.

into diketopiperazine (**3**) by bromination followed by treatment with zinc dust and acetic acid⁴: 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 $C_{12}H_{20}N_5OBr \cdot HBr$: 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: $\lambda_{max}^{H_2O}(\epsilon)$ 333 m μ (15,400), 236 m μ (15,700); NMR spectrum (D_2O , 60 MHz): δ 1.01 [6H, d, J ~6Hz, $(CH_3)_2-CH$], 1.9~2.4 (3H, m, H-8 and CH_2-10), 2.70 (2H, d, J 8Hz, CH_2-7), 2.91 (2H, t, J 8Hz, CH_2-9), 3.41 (2H, t, J ~7Hz, CH_2-11). The signal of H-5 was no longer 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 diacetyl-positive single spot (Rf 0.4) on TLC with cellulose "Avicel" and Solvent I, was chro-

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

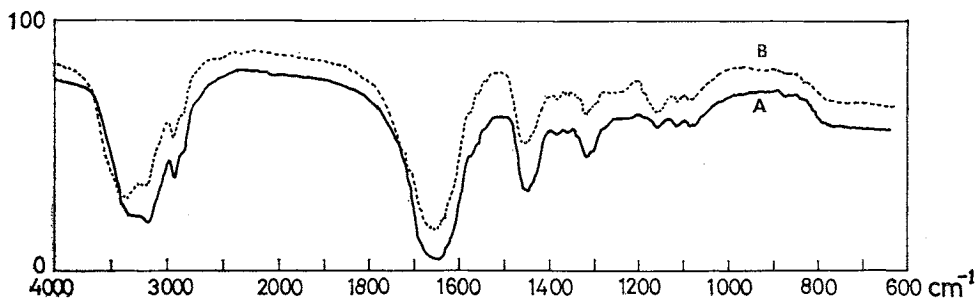


Fig. 2. NMR spectra of **3**(upper) and **3'** hydrochlorides(lower) in $DMF-d_7$ at 100 MHz.

