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FIRST TOTAL SYNTHESIS AND NMR DATA OF THE STRYCHNOS ALKALOID 19,20-DIHYDROAKUAMMICINE

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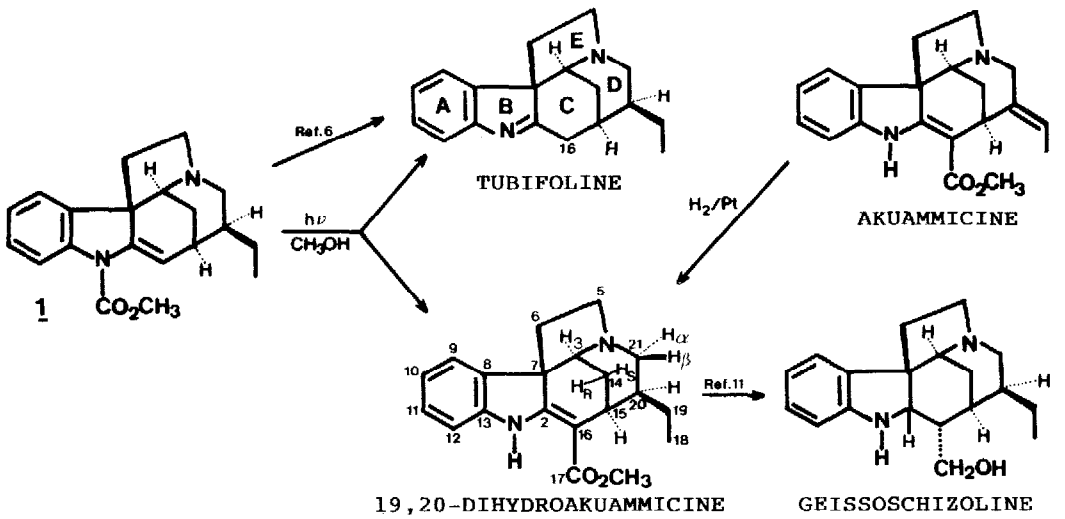
The first total synthesis of the Strychnos indole alkaloid 19,20-dihydroakuammicine and detailed ^{1}H- and ^{13}C-NMR data of this alkaloid are reported.

The pentacyclic Strychnos indole alkaloid 19,20-dihydroakuammicine was isolated[1] for the first time by Schmid from the leaves of Pleiocarpa tubicina Stapf. Before its isolation, 19,20-dihydroakuammicine was a known compound which had been obtained by partial synthesis[2] in the context of chemical correlations effected for structural elucidation of other Strychnos[3] alkaloids. However, no total synthesis of 19,20-dihydroakuammicine has been recorded so far.

Recently, we have reported a new synthetic strategy[4] for the elaboration of the pentacyclic skeleton of Strychnos alkaloids based on the closure of the five membered E ring in the last steps of the synthesis. This strategy has been successfully applied to the total synthesis of (±)-tubifolidine[5] and (±)-tubifoline,[6] two alkaloids lacking the oxidized one-carbon substituent



present at C-16 in the greater part of Strychnos alkaloids. Thus, it was of interest to develop a procedure for the introduction of this carbon unit on the pentacyclic Strychnos skeleton so that our synthetic strategy could constitute a general entry to the more complex alkaloids of this group. An inspection of the methods previously used for the introduction of the C-16 methoxycarbonyl group in the Aspidosperma series[7-9] led us to choose that reported by Wenkert[8] consisting in the photochemical rearrangement of a N_a-methoxycarbonyl-α-methyleneindoline derivative to the corresponding vinylogous urethane.[10] This was envisaged as the most straightforward procedure since we had in hand the required N-methoxycarbonylenamine **1**, an intermediate in our synthesis of (±)-tubifoline.[6]

Irradiation of a methanolic solution of compound **1** with a high-pressure mercury lamp for 60 min afforded a mixture of (±)-19,20-dihydroakuammicine (20% yield) and the corresponding decarbomethoxylated product, (±)-tubifoline (13% yield). In all assays small amounts of the starting material were recovered. Given that 19,20-dihydroakuammicine had been previously converted into geissoschizoline,[11] the synthesis here reported also constitutes a formal total synthesis of the latter alkaloid.[12,13] 19,20-Dihidroakuammicine was identified by comparison (TLC)[1,14] with a sample obtained by catalytic hydrogenation of akuammicine[2a,b] and by its high resolution ^{1}H- and ^{13}C-NMR spectra, which are reported for the first time in this paper.

The assignment of the NMR signals of 19,20-dihydroakuammicine was effected with the aid of the heteronuclear shift correlated 2D-NMR spectrum and DEPT (^{13}C-NMR) experiments, taking into account the established data for related Strychnos indole alkaloids.[15] The ^{13}C-NMR spectrum of 19,20-dihydroakuammicine (Table 1) showed all the carbon resonances at the expected values. Thus, the signals at δ168.6, 98.6, 170.5, and 51.0 were assigned to the C-2, C-16, C-17, and OCH_3 carbons, respectively, confirming the presence of an anilinoacrylate moiety. On the other hand, the most significant signals in the ^{1}H-NMR spectrum (Table 2) were a broad singlet at δ9.03 assigned to the N-H proton of the indoline ring and a singlet at δ3.75 corresponding to the methoxy protons of the ester group (compare with δ5.98 (d, J=7.5 Hz) and 3.92 for the vinyl and methoxy protons, respectively, in the starting urethane **1**). These data and the presence of signals attributable to four aromatic protons corroborated that the photochemically induced 1,3-acyl shift had taken place in the expected way. Moreover, the presence of a methoxycarbonyl group at the C-16 position induces the shielding of one of the diastereotopic C-19 methylene protons as compared with **1** and other pentacyclic systems (tubifoline,[6] tubifolidine[5]) lacking this substituent. Finally, as it is characteristic in the ^{1}H-NMR spectra of Strychnos alkaloids, the most deshielded signal of the aliphatic region is a broad singlet corresponding to the methine H-3 at δ3.95.

TABLE 1. ^{13}C-NMR Data of 19,20-Dihydroakuammicine[a]

C-2...168.6	C-10..121.2	C-17..170.5
C-3....60.8	C-11..127.9	C-18...11.4
C-5....53.3	C-12..109.8	C-19...25.8
C-6....42.0	C-13..144.2	C-20...38.7
C-7....55.5	C-14...30.8	C-21...50.8
C-8...134.4	C-15...30.3	CH_3O...51.0
C-9...119.7	C-16...98.6	

[a]In ppm relative to TMS. Measured in $CDCl_3$ solution. 75 MHz.

TABLE 2. ^{1}H-NMR Data of 19,20-Dihydroakuammicine[a]

H-3	3.95 br s	H-14S	2.06 dt (12.5, 3.0)
H-5α	3.10 td (12.0, 6.8)	H-15	3.15 m
H-5β	2.80-3.00	H-18	0,90 m
H-6α	1.95 dd (12.5, 6.8)	H-19	0.95 and 1.25 2m
H-6β	2.80-3.00	H-20	1.85 m
H-9	7.15 d (7.3)	H-21α	3.00 dd (12.5, 6.5)
H-10	6.89 t (7.3)	H-21β	2.05 t (12.5)
H-11	7.12 t (7.3)	CH_3O	3.75 s
H-12	6.80 d (7.3)	N-H	9.03 br s
H-14R	1.40 dt (12.5, 3.0)		

[a]In ppm relative to TMS. Measured in $CDCl_3$ solution. Values in parentheses are coupling constants in Hz. 300 MHz.

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