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STUDIES ON THE SYNTHESIS OF AKUAMMILINE-TYPE ALKALOIDS. CONSTRUCTION OF THE HEXAHYDRO-1,5-METHANOAZOCINO[3,4-b]INDOLE FRAGMENT

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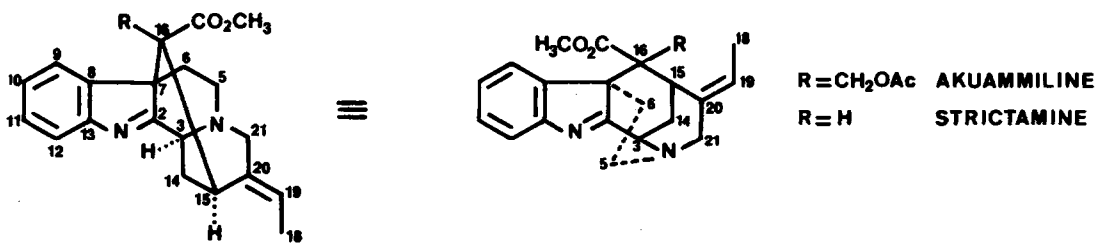
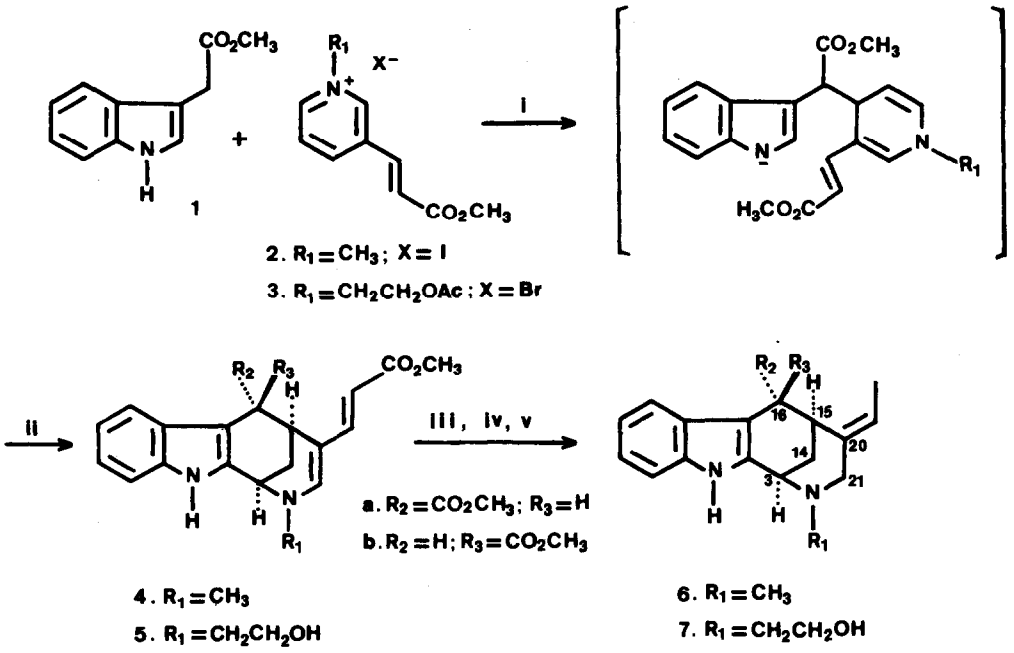
A three step route to the title tetracyclic substructure of akuammiline-type alkaloids consisting in the nucleophilic addition of an ester α-anion to an N-alkylpyridinium salt, acid-induced cyclization of the resultant 1,4-dihydropyridine, and stereoselective elaboration of the ethylidene substituent is reported.

The indole alkaloids of the akuammiline group[1] (e.g. akuammiline, strictamine) have, as common structural features, a carbon skeleton formally derivable from the corynantheine type by the introduction of an extra carbon-carbon bond between C-7 and C-16,[2] an ethylidene E-configurated substituent at C-20, and one or two substituents with a functionalized one-carbon atom at C-16. No synthesis for these alkaloids, not even for model systems having their pentacyclic skeleton, has been reported so far.

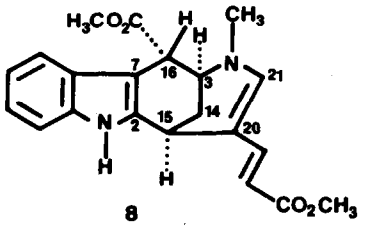
We present here a short and efficient synthetic route to the hexahydro-1,5-methanoazocino[3,4-b]indole systems **6** and **7**, which possess four[3] of the five rings of the alkaloids strictamine and akuammiline and incorporate their characteristic C-16 and C-20 appendages. Moreover, compound **7** bears a functionalized two-carbon chain (C-5 and C-6 in the biogenetic numbering) on the piperidine nitrogen. The synthesis involves intermolecular addition of a stabilized carbon nucleophile to the γ-position of an N-alkylpyridinium salt,[4] regiospecific acid promoted cyclization of the resulting 1,4-dihydropyridine, and stereoselective elaboration of the E-ethylidene group.[5] We employed a similar three-step reaction sequence in the first total synthesis of the bridged indole alkaloid vinoxine[6] and in the preparation of 4-ethylidene-hexahydro-1,5-methanoazocino[4,3-b]indoles.[7]





Reagents: (i) LDA, THF, -30°C, 1 h; (ii) C_6H_6-HCl, r.t., 4 h; (iii) 4N HCl, 100°C, 2 h; (iv) 1.5N MeOH-HCl, r.t., 18 h; (v) $NaBH_4$, MeOH, 0°C, 1 h

Treatment of pyridinium salt **2**[8] with the dianion derived from ester **1**[9] and then with acid afforded tetracycle **4a**[10,11] in 31% yield (only trace amounts of the corresponding 15-H/16-H cis-isomer **4b** were detected). The unexpected regioisomer **8**,[12] formed by nucleophilic attack to the α-position of the pyridinium salt followed by acid-catalyzed cyclization of the resulting 1,2-dihydropyridine, was obtained as by-product (15% yield). When the above two-step sequence was effected from pyridinium salt **3**,[6] tetracycle **5**[13] was obtained (11%) as a 3:1 mixture of C-16 epimers, **5a** and **5b** respectively.



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Further stereoselective elaboration of the E-ethylidene substituent was effected taking advantage of the doubly vinylogous urethane moiety of tetracycles **4** and **5**. Thus, treatment of **4a** with refluxing 4N hydrochloric acid brought about both the hydrolysis of ester groups and the decarboxylation of the resulting tetrahydro-3-pyridylacrylic acid to give a conjugated iminium ion which, after reesterification of the 16-carboxy group, was reduced with sodium borohydride.[14] A C-16 epimeric mixture of ethylidene derivatives **6a**[15] and **6b**[15] (3:1 ratio) was obtained in 40% yield. Similarly, a mixture of tetracycles **5a,b** was converted to **7a,b**[16] in 50% yield.

The most significant ^{13}C-NMR chemical shift values of tetracycles prepared in this work are listed in Table 1.

TABLE 1. Significant ^{13}C-NMR Chemical Shifts of Tetracycles 4-8[a]

	4a[b]	5a[b]	5b[b]	6a[c]	6b[c]	7b[c]	8[b]
C-3	48.9	47.9	47.5	53.2	53.2	51.3	53.9
C-14	25.5	25.6	28.6	29.9	33.3	33.4	25.4
C-15	28.8	29.1	28.6	31.4	31.3	32.0	24.7
C-16	42.4	42.3	46.5	43.2	43.0	44.7	42.2
C-21	146.3	146.6	148.5	56.0	56.7	55.2	145.3

[a] In ppm relative to TMS at 50.3 MHz. [b] In DMSO-d_6 solution. [c] In $CDCl_3$ solution

Compounds **7a,b** can be envisaged as synthetic precursors of strictamine. The N-hydroxyethyl substituent can allow further closure of the tryptamine unit by formation of C_6-C_7 bond. Although attempts to induce a similar ring closure from a model hexahydro-1,5-methanoazocino[3,4-b]indole system lacking C-16 and C-20 substituents were unsuccessful,[3a] we have recently reported closely related cyclizations of N-[bis(methylthio)ethyl]-hexahydro-1,5-methanoazocino[4,3-b]indoles to pentacyclic Strychnos-type systems.[17] Further work on the synthesis of alkaloids of the akuammiline group is in progress in our laboratory.

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