Nineteen new tertiary amines are described along with their hydrochloride, methiodide or sulfate salts. Also one new hydrocarbon is reported. All reaction products were characterized by elemental (C, H, N) and spectral (ir and nmr) analyses. Order No. 74-21,140, 102 pages.

PART ONE: STUDIES DIRECTED TOWARD A NEW SYNTHESIS OF LYSERGIC ACID. PART TWO: THE CYCLIZATION 1-(4-METHOXY-2,6-d_2-BENZYL)-2-METHYL-1,2,3,4,5,6,7,8-OCTAHYDROISOQUINOLINE

WU, Wuu-Yong, Ph.D.
The University of Rochester, 1974

I: The synthesis of lysergic acid (3a) by reversal of the acid catalyzed isomerization of lysergic acid to 8-carboxy-6-methyl-1,2,6,7,8,9-hexahydroindolo[4,3-fg]-quinoline (4a) has been unsuccessfully attempted in the past. The pi electron system of 3a converts to the more stable naphthalene system and the isomerization is essentially irreversible. The purpose of this work was to investigate the possibility that in suitably constructed substances, such as 8-keto-6-methylergoline-9-ene (9), the position of this equilibrium might be reversed and that therefore the naphthalene system of 8-keto-6-methyl-1,2,6,7,8,9-hexahydroindolo[4,3-fg]-quinoline (8) might be convertible to 9 by isomerization.

The compound 8 was to be synthesized from its precursor 8-hydroxy-6-methyl-1-N-acetyl-1,2,6,7,8,9-hexahydroindolo-[4,3-fg]-quinoline (28) by oxidation of the alcohol function to a ketone. The preparation of 2-hydroxy-4-methyl-7-amino-1,2,3,4-tetrahydrobenzo[f]-quinoline-6-carboxylic acid lactam, an intermediate in the preparation of 28, was repeated. The synthesis of the precursor 28 was achieved but the synthesis of ketone compound 8 was not realized.

II: Cyclization of 1-(4-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline with phosphoric acid as catalyst has been found to yield about 96% of cis-morphinan derivative and less than 4% of the trans isomer. When aluminum bromide is used as catalyst, the cyclization resulted in a yield of ca. 28% of the trans product.

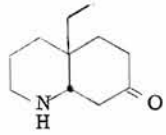
The purpose of this work was to ascertain if an intramolecular hydrogen transfer mechanism is possible in this cyclization reaction. The deuterated compound, 1-(4-methoxy-2,6-d_2-benzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline was synthesized and cyclized with aluminum bromide. Mass spectrometric analysis revealed that the percentages of the deuterated compounds of cis and trans product are quite close, and natural abundance C-13 nmr spectra also indicate that deuterium is lost rather than transferred. Hence, the effect of aluminum bromide on the cyclization may result from coordination of the catalyst with basic nitrogen to simply force preferential protonation on the side cis to the benzyl group and thus result in the formation of more trans product.
Order No. 74-22,641, 122 pages.

SYNTHETIC PATHWAYS TO THE ASPIDOSPERMA ALKALOID RING SYSTEM

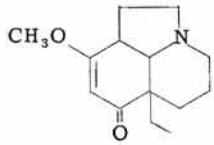
ZIMMERMAN, Robert LeRoy, Ph.D.
Rice University, 1973

Two synthetic pathways to the Aspidosperma ring system are presented. A study of a third pathway is also presented. Key reactions in these pathways include a cyclopropyl imine rearrangement to a Δ^2-pyrroline and/or a methyl vinyl ketone annelation of an endocyclic enamine.

The first pathway uses the methyl vinyl ketone annelation to a 2-piperideine to give a hydroquinolone system.



The second pathway uses a cyclopropyl imine rearrangement in the generation of a hydrolulodidone system.



The third sequence is a study using both the cyclopropyl imine rearrangement and the methyl vinyl ketone annelation to generate the Aspidosperma ring system.
Order No. 74-21,350, 118 pages.

CHEMISTRY, PHARMACEUTICAL

CENTRAL NERVOUS SYSTEM CARBONIC ANHYDRASE INHIBITORS

LUKES, James John, Ph.D.
The University of Connecticut, 1974

With the presence of the enzyme carbonic anhydrase firmly established within the glial cellular elements of the brain and its absence from the brain's neuronal cellular elements also concluded, this research effort resulted in the design and synthesis of a series of compounds related to the carbonic anhydrase inhibitor, methazolamide, and examined the capacity of such derivatives to inhibit carbonic anhydrase of brain in vitro and in vivo.

This study presented the synthetic procedures utilized in the preparation of a series of 2-(trimethoxybenzoylimino)-3-methyl-Δ^4-1,3,4-thiadiazole-sulfonamides and of 2-(parahalobenzoylimino)-3-methyl-Δ^4-1,3,4-thiadiazolinesulfonamides. The various synthetic schemes and the modifications required to accomplish each process were elucidated.

Methazolamide, which had been shown to possess the highest pKa value of those compounds synthesized for use as carbonic anhydrase inhibitors in previous studies, had also displayed the best penetration and the highest localization within brain tissue. Determinations of the pKa values for the synthesized derivatives were performed in this study in order to establish a possible relationship between the pKa value and the distribution and diffusibility characteristics of the synthesized compounds toward brain tissue. Each of the synthesized compounds possessed a pKa which was greater than that of the reference compound methazolamide (literature pKa 7.3). The greater pKa value in the synthesized compounds would allow more of the unionized form to be available for greater penetration, diffusibility and distribution within brain tissue for inhibition of the contained carbonic anhydrase enzymic activity.

The compound 2-(2',4',5'-trimethoxybenzoylimino)-3-methyl-Δ^4-1,3,4-thiadiazoline-5-sulfonamide in this series possessed the highest pKa value and the lowest molar concentration as its in vitro I_{50} value. It also possessed the lowest $E.D._{50}$ value in