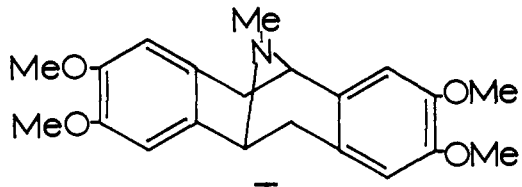
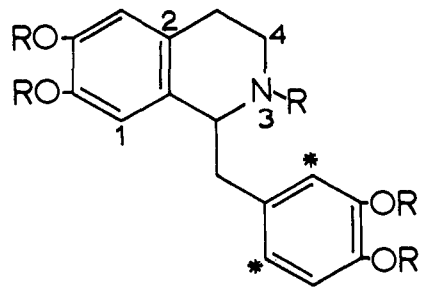
A search of the literature showed that the physical characteristics of argemonine matched fairly closely with those of the N-methyl derivative of pavine, an optically inactive base obtained by the reduction of papaverine with tin and hydrochloric acid.[4a-c] Extensive chemical characterization[5a,b] had showed that N-methylpavine has the structure I. The degradative work on argemonine[1a-e] parallels that on N-methylpavine[5b] step for step and, in particular, both series lead, by the same processes, to a nitrogen-free compound of m.p. 156°, identified[5b] as 2,3,8,9-tetramethoxy-5,6-dihydrodibenzo[*a*,*e*]cycloöctene.

We have prepared N-methylpavine using the procedure of Pyman[4c] and have compared it with (−)-argemonine from *A. munita*.[6] The ultraviolet and solution infrared spectra of the two are identical and the structural identity of these bases is thereby confirmed.

This is the first report of the nitrogen-bridged tetrahydrodibenzocycloöctene system in a natural product and the structure presents a novel problem in alkaloid biosynthesis. Most current biogenetic hypotheses for Papaveraceous alkaloids depict a benzyltetrahydroisoquinoline (II) as a key intermediate which can couple from the asterisked positions to positions 1, 2, or 3 to furnish the aporphine, morphine, or cyptaustoline series of alkaloids. Argemonine coud fit into this scheme if a coupling occurred to position 4. If the precursor is



I



II

similar to laudanosine (II, R = CH_3), then argemonine would be the primary alkaloid in this series and successive O-demethylations would lead to nor- and bisnorargemonine. This would be in keeping with the demethylation series (thebaine to codeine to morphine) shown to occur in the opium poppy.[7] Biosynthetic studies are currently underway to test these and other possible pathways of metabolism in this new series of plant alkaloids.[8]

Acknowledgment.—This investigation was supported by Public Health Service Research Grant RG-9300, Division of General Medical Sciences. We also wish to acknowledge the helpful suggestions of the students in Chem. 227 at Utah State University in 1962 who struggled with the structure of argemonine as a literature and term paper assignment.

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RECEIVED MARCH 11, 1963

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STEREOCHEMISTRY AND SYNTHESIS OF AMOSAMINE: 4,6-DIDEOXY-4-DIMETHYLAMINO-D-GLUCOSE

Sir:

This communication reports the complete identification and synthesis of the first 4-aminosugar isolated from natural sources. 3-Aminosugars such as mycaminose,[1,2] mycosamine[3] and desosamine[4-6] have been investigated as important moieties of certain antibiotics. Amosamine,[7,8] the aminosugar moiety of the antibiotic amicetin,[9,10] is shown by synthesis in this investigation to be 4,6-dideoxy-4-dimethylamino-D-glucose.

One of the most significant properties of amosamine is its basicity. The free sugar, the α and the β methyl glycoside, the disaccharide amicetamine and the antibiotic amicetin have pK'_a values close to 7, which represent a tenfold decrease in basicity when compared with the 3-dimethylaminosugars mycaminose[11] and desosamine.[12] These data and the degradation studies reported earlier required the consideration of a 4-amino structure and an examination of the molecular rotation values of amosamine and the α and β methyl glycosides indicated the stereochemistry of the glucose series as a likely possibility. Synthesis of the crystalline methyl 4,6-dideoxy-4-dimethylamino-α,D-glucopyranoside (VI), the free sugar and the crystalline itol hydrochloride, identical with the natural material, confirmed these considerations.

The starting material for the synthesis was I, a known 4,6-ditosylate derivative of D-galactose.[13] Selective displacement of the 6-tosyl group with sodium iodide to give the 6-iodo derivative II, m.p. 131.5–133°, was accomplished in acetone solvent at 105–110°. II was separated from unreacted I and diiodo by-product by column chromatography over alumina. The 6-iodo derivative II was reduced to the 6-deoxy derivative III, m.p. 157–158.5°, using Raney nickel catalyst in the presence of a few drops of sodium hydroxide solution. The 4-tosyl group of III was displaced with azide ion in refluxing dimethylformamide to give the glucose derivative IV, which was not isolated but converted by successive treatment with hydrogen in the presence of plati-

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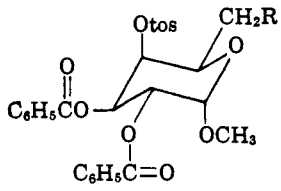
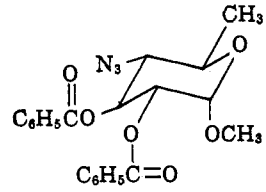
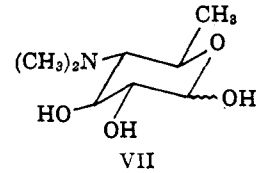


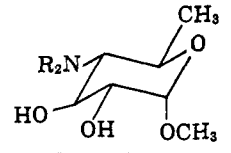
I R = Otos
II R = I
III R = H



IV



VII



V R = H
VI R = CH_3

num catalyst, barium hydroxide and then formic acid–formaldehyde into the crystalline α-methyl glycoside of amosamine VI, identical with the natural product by mixture melting point determination and examination of the infrared spectra, which were superimposable. Hydrolysis of the α-methyl glycoside gave the free sugar, 4,6-dideoxy-4-dimethylamino-D-glucose (VII), which traveled with the same R_f values as amosamine upon paper chromatography in a pyridine–ethyl acetate–water (5:12:4) system and in a pyridine–ethyl acetate–acetic acid–water (5:5:3:1) system. The free sugar VII was converted to the itol VIII using sodium borohydride. The crystalline itol hydrochloride was identical with the natural derivative as shown by mixture melting point determination and paper chromatographic comparisons.

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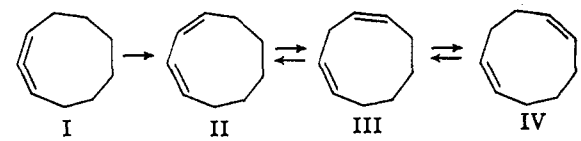
BASE-CATALYZED ISOMERIZATION OF MEDIUM RING DIENES AND TRIENES[1]

Sir:

The observation that dimethyl sulfoxide enhances the base strength of potassium *t*-butoxide has led to rather extensive use of this system for carbanion reactions.[2] Noteworthy applications are the recently described isomerization of 2-methyl-1-pentene[3] and the study of *endo* ⇄ *exo* kinetics with alkylidenecycloalkanes.[4] While these studies dealt primarily with isomerization rates, equilibrium compositions appeared to be in qualitative agreement[4] with data available from other investigations. The present investigation was in fact initiated on the premise that product ratios would reflect relative thermodynamic stabilities of the isomers.

The thermal isomerization of allenes to mixtures of acetylenes and 1,3-dienes is well known.[5] More recently, 1,2-cyclodecadiene was reported to undergo isomerization to 1,3- and 1,4-cyclodecadiene when heated at 190° in diethyl carbitol containing potassium hydroxide.[6]

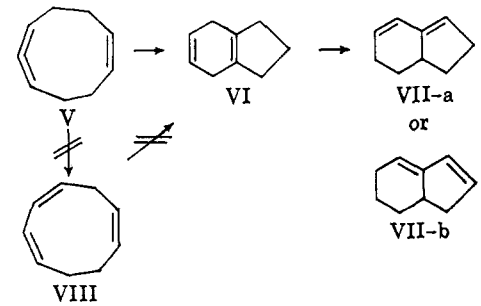
We have found that 1,5-cycloöctadiene is converted rapidly and essentially quantitatively to 1,3-cycloöctadiene by potassium *t*-butoxide in dimethyl sulfoxide (1 hr., 70°). Similarly, 1,2-cyclononadiene (I)[7] under identical conditions gave rise to 1,3-cyclononadiene (II) which is 98% pure by vapor–liquid chromatography. The properties of II are in good agreement with those reported.[8] Extending the reaction time to 3 hr. afforded a mixture comprised of 70% of II and 23% and 7% of two new substances. The first of these was separated by vapor–liquid chromatography as 97–98% pure material. Quantitative microhydrogenation required two mole-equivalents of hydrogen and gave cyclononane, identified by comparisons of its chromatographic retention time and infrared spectrum with those of authentic material. Ozonolysis afforded malonic acid and adipic acid which, as a mixture, were converted to their methyl esters and identified chromatographically. It is thus clear that this substance is 1,4-cyclononadiene (III).[9] Very strong infrared absorption at 13.5 μ suggests that both double bonds are *cis*. The second of the two new compounds was shown to be *cis,cis*-1,5-cyclononadiene (IV) by the usual comparisons with a sample prepared by an independent synthesis.[9,10] Equilibration experiments (144 hr., 70°) using either I or IV gave the same equilibrium composition: 94% IV, 6% II and only a trace of III. *It thus would appear that cis, cis-1,5-cyclononadiene (IV) is, by a substantial margin, the most stable of the isomeric cyclononadienes.* The typical 1,3-diene stability is lacking in II as a result of the large interplanar angle imposed by ring strain.



I II III IV

The isomerization of 1,2,6-cyclononatriene (V)[7] for 2 hr. (70°) gave a mixture of two products which was easily separated by vapor–liquid chromatography. The minor component (40%) proved to be 4,7-dihydroindane (VI) when comparison was made with authentic material.[11] The major product (60%) gave a mixture of hexahydroindane and tetrahydroindane upon catalytic hydrogenation. It can be formulated as either bicyclo[4.3.0]nona-1,8- or 4,6-diene (VIIa or b) on the basis of its ultraviolet spectrum (λ_{max}^{EtOH} 236 mμ, ϵ 15,000) and n.m.r. spectrum (3 vinyl protons).

Two short-lived intermediates in the V → VI isomerization have been detected. It appeared likely that one of these might be 1,3,5-cyclononatrienes an



V VI VII-a or VII-b VIII

(1) The authors are indebted to the Robert A. Welch Foundation for the financial support of this study. Generous quantities of cycloöctene, 1,3-cycloöctadiene and 1,5-cycloöctadiene were kindly provided by the Petrochemical Research Laboratory, Cities Service Research and Development Co., Lake Charles, La.

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