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ANGUSTMYCIN A AND DECOYININE

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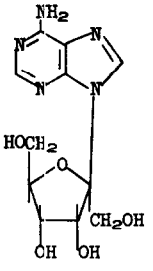
Angustmycin C (1)[1] and psicofuranine[2] have been reported to be identical.[3,4] Yüntsen et al. also reported isolating a second adenine hexoside, angustmycin A. The psicofuranine fermentations have also produced an additional adeninehexoside, decoyinine.[5] While no direct comparison of samples has been made, a number of published data suggest that decoyinine and angustmycin A may be identical. The empirical formula, $C_{11}H_{13}N_5O_4$, melting points of the hydrate, methanol or ethanol solvate and triacetate, and the infrared curves all attest to this.

The angustmycin A structure was reported[6] to be 2. Data accumulated in this laboratory are in disagreement with the assignment of this structure to decoyinine, but instead favor 3. Foremost of these is the fact that the N.M.R. spectra of decoyinine and its derivatives show the absence of a C-methyl group, which for 2 would be expected as a doublet at about 1.38 δ. Outside of solvent absorbance, the decoyinine spectrum (Fig. 1) showed no absorbance below 247 c.p.s., measured downfield from TMS at 60 mc. Kuhn-Roth determinations were extremely variable in our hands, but usually indicated less than 10% of one C-methyl group. Furthermore, although hydrolysis of structure 2 should give fucosone, the decoyinine sugar decomposed during both mild hydrolysis and methanolysis, and could not be isolated in a pure state, nor could the usual carbonyl derivatives be made. Periodate titrations were

atypical, due to iodoform precipitation during the iodine titration, with rapid fading of endpoints.

Fermentation data[7] were also unfavorable for structure 2, suggesting a closer structural relationship to psicofuranine. When radioactive decoyinine was added to a fermentation with S. hygroscopicus, var. decoyicus, in a suitable medium, it was converted to a psicofuranine-decoyinine equilibrium mixture which could also be reached by psicofuranine addition. Appropriate labeling showed that these equilibrations occurred without cleavage between the purine and the respective sugars.

Thus it becomes necessary to reexamine the reactions reported for angustmycin A and find an alternate interpretation. In Chart I the data reported by Yüntsen are reinterpreted in the light of structure 3. Compounds 4, 5, 8, 13, and formic acid are the ultimate degradation products which could be explained by either 2 or 3. As shown in the chart these products arise from 3 through intermediates 7, 9, 10, 11, and 12, which are new structures replacing Compounds XII, XVII, XX, XXI, and XXII, the respective intermediates reported from structure 2.*



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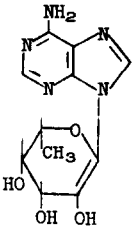

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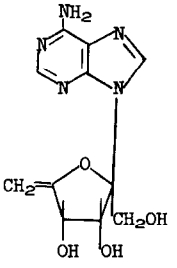

3

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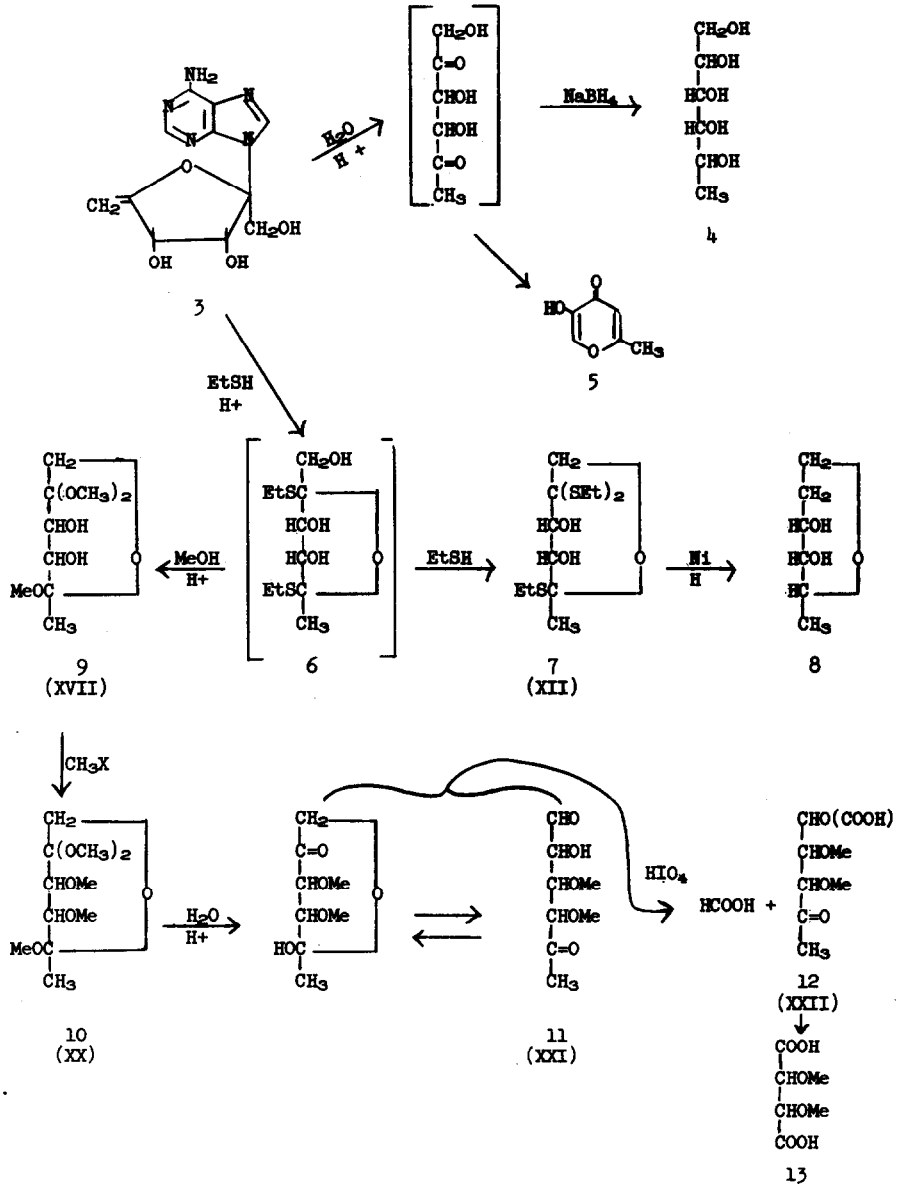
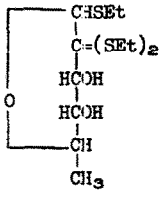
* The Roman numbering corresponds to the numbering found in reference 6.

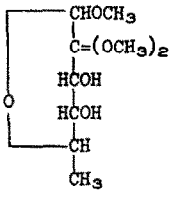
CHART I

Reinterpretation of Yüntsen's Reactions Based on the Alternative Structure 3*

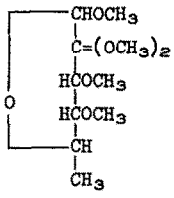




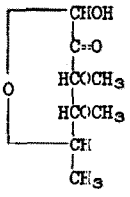
XXI



XVII



XX



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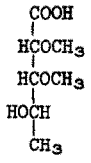


XXII

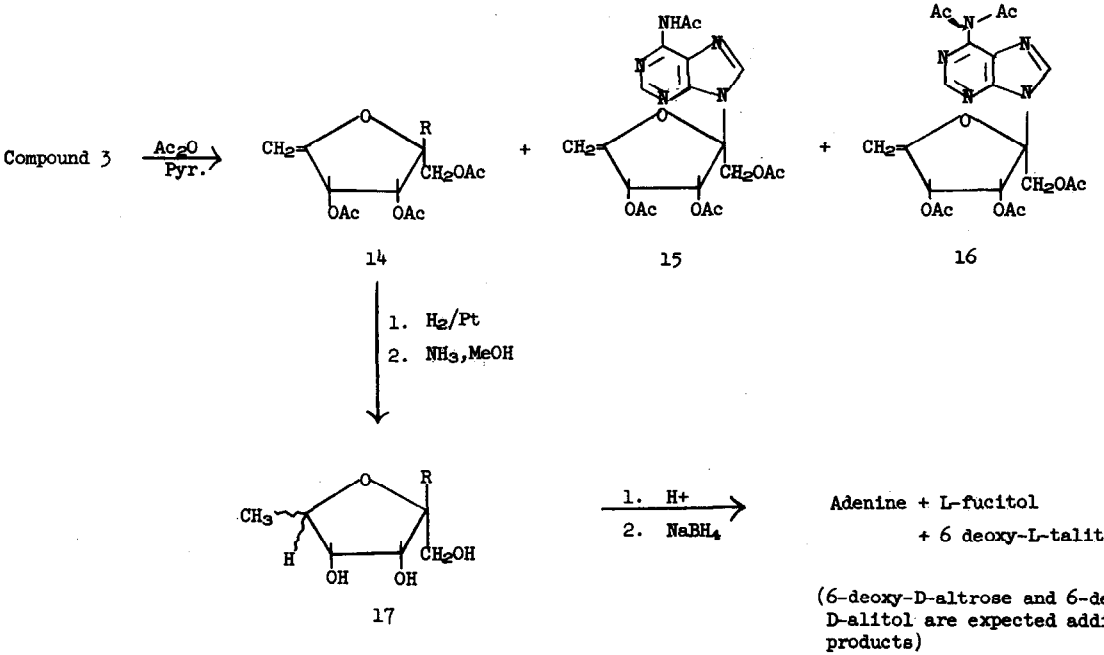
Acetylation of angustmycin A gave a tetraacetate (II*), m.p. 187-188°. As shown in Chart II, the same procedure, acetic anhydride in pyridine, applied to decoyinine provided a triacetate (14), m.p. 188-190°. With an excess of acetylating agent decoyinine gave a mixture which, when separated by countercurrent distribution, yielded the tetraacetate (15), m.p. ca. 65°, and the pentaacetate (16), m.p. 152-153°. The number of acetyl functions was confirmed by the N.M.R. spectra; the triacetate (Fig. 2) having three singlets of appropriate area at 1.92, 2.10, and 2.23 δ (and NH_2 absorbance at 6.23 δ); the tetraacetate having the same three plus one additional broader singlet at 2.43 δ; and the pentaacetate (Fig. 3) having the same four singlets, with the least shielded one (2.43 δ) shifted upfield slightly to 2.36 δ and now having an area corresponding to 6 hydrogens. (The magnetic equivalence of the six N-acetyl hydrogens strongly suggests that the two acetyl groups are on the same nitrogen.)

The N.M.R. spectra of decoyinine and its acetates taken individually are

CHART II

Acetylation and Reduction of Structure 3

R = 9-Adenyl

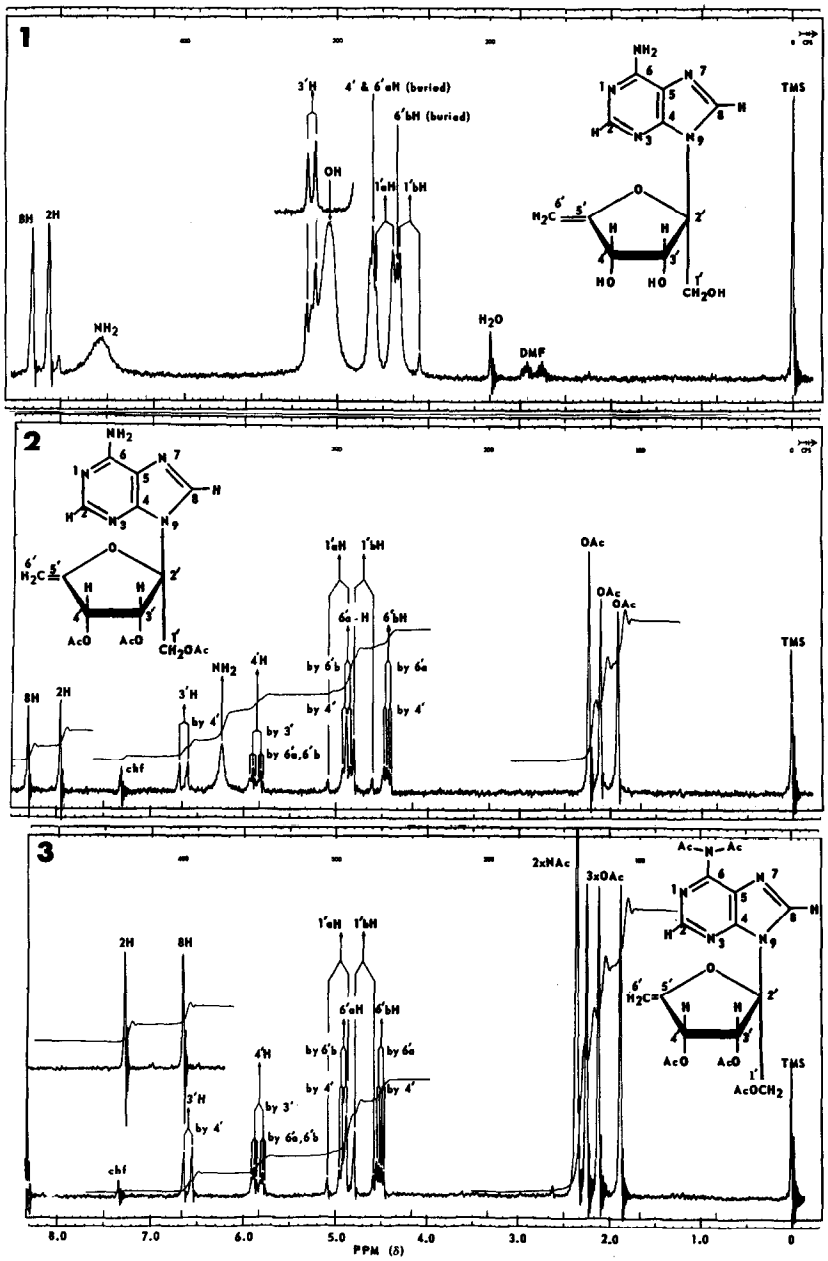


difficult to interpret because of the overlapping of some absorbances. However, acetylation of the hydroxyl groups results in differential shifting of the primary and secondary hydrogen peaks. This uncovers sufficient absorbances to permit a clear interpretation when all the spectra are considered together.

In the spectrum of the triacetate (Fig. 2) there are two vinyl hydrogens characteristic of a terminal methylene group and four carbinol hydrogens, all in addition to the three acetate and the adenine absorbances. The carbinol hydrogen doublet at 6.65 δ** is coupled with a J of 5 c.p.s. to one cis neighboring carbinol hydrogen at 5.86 δ. This 5.86-δ multiplet is actually two sets of triplets owing to the 1.8-c.p.s. long-range coupling through the double bond to the two methylene hydrogens. These methylene hydrogens are in turn identified from their splittings of 1.8 c.p.s. by the carbinol hydrogen and 3 c.p.s. by each other as expected and are found at 4.44 and 4.88 δ. The remaining AB multiplet in the carbinol region is attributed to the hydroxymethylene group. These two hydrogens show a coupling characteristic of two hydrogens on the same carbon atom which is not freely rotating and which is isolated from the rest of the system.

Platinum-catalyzed hydrogenation of angustmycin A tetraacetate followed by deacetylation gave dihydroangustmycin A (IV*).[6] Similar treatment of decoyinine triacetate gave dihydrodecoyinine (17). A considerable quantity of hydrogenolyzed material was separated from the hydrogenation product by countercurrent distribution. Kuhn-Roth analyses agree for one C-methyl group. Compound 17 does display the C-methyl function in the N.M.R. The spectrum (Fig. 4) actually shows a pair of C-methyl doublets at 1.36 and 1.42 δ, each having a J of 6.5 c.p.s. corresponding to the two stereoisomers at C-5'. This isomerism at C-5' is also reflected in the absorbance frequency of the nearby aromatic hydrogen, which is observed either at 8.10 or 8.20δ depending on the

** As in psicofuranine, the unshielding of this hydrogen is attributed to anisotropy effects of the nearby purine ring system.



NMR Spectra. 1. Decoyinine in d7-Dimethylformamide; 2. Triacetate of Decoyinine in Deuteriochloroform; 3. Pentaacetate of Decoyinine in Deuteriochloroform.

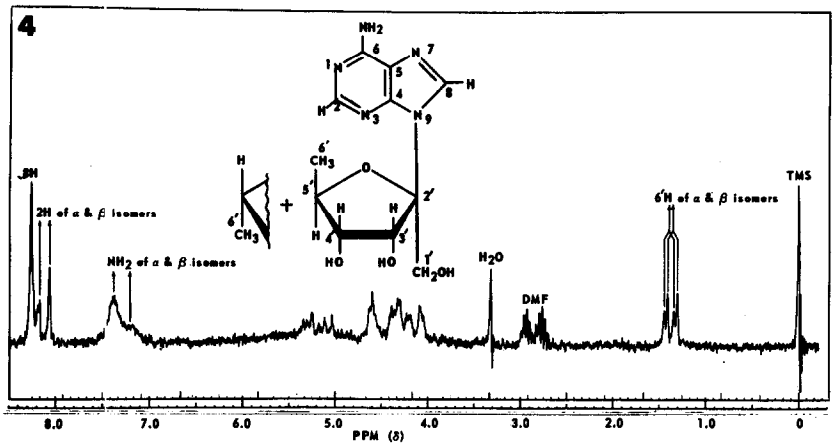


Figure 4. Isomeric Dihydrodecoyinines in d_7-Dimethylformamide

methyl orientation. One of the isomers was separated by crystallization and the NMR spectrum of it (not shown) clearly showed the new methyl as one doublet and the new carbinol hydrogen produced on hydrogenation as a doublet of doublets at 3.8 and 4.05δ, J = 12 cps.

On acid hydrolysis of compound 17, no trace of fucose, expected if 2 were the formula, was detected. But, as in the case of dihydroangustmycin A, after acid hydrolysis and a sodium borohydride treatment, it did afford L-fucitol and 6-deoxy-L-talitol, the product expected from the L-isomer. Furthermore, compound 17 consumed just one mole of periodate. With Drury's orcinol-ferric chloride test[8,9] the hydrolytic mixture showed ultraviolet maxima at 420 and 520 mμ and with the cysteine-carbazole test[8,10] the maximum at 545 mμ was seen, suggesting a methyl ketopentose, expected from 17.

Ozonolysis of decoyinine in glacial acetic acid gave a 36% yield of formaldehyde, isolated as the dimedon derivative. Psicofuranine, used as a control, gave no formaldehyde under these conditions. This is the predicted product from structure 3, but not from 2.

These new data, combined with the data in the literature, support structure 3, which we now propose as the preferred tentative structure for this compound. The choice of the β-linkage of the sugar is based only on the analogy to psicofuranine.

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