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SYNTHESIS OF ANHYDROSIBIROMYCINONE: A NEW METHOD FOR THE DIRECT SYNTHESIS OF PYRROLO-1,4-BENZODIAZEPIN-5-ONES

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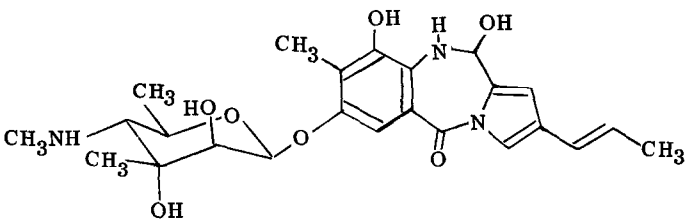
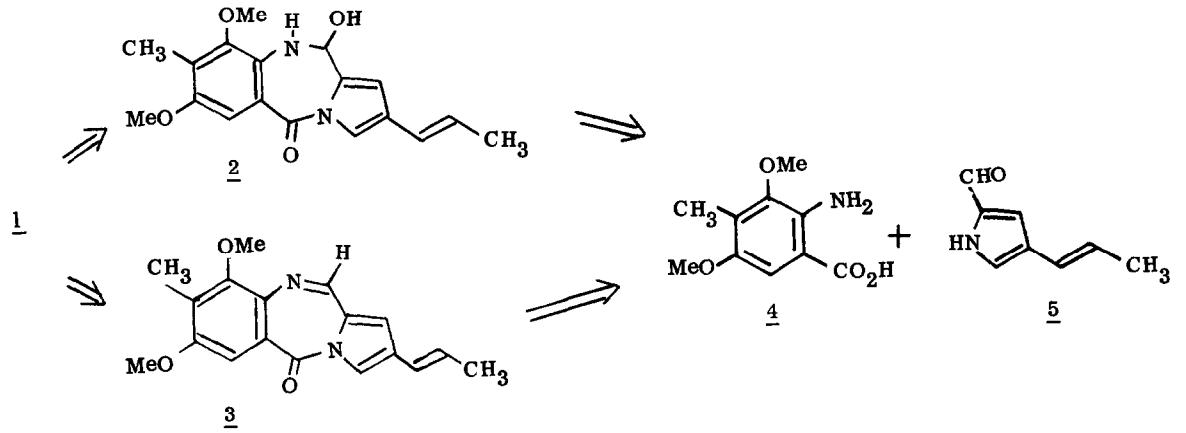
Dimethylanhydrosibiromycinone (3) was prepared by the condensation of pyrrole aldehyde 5 with the sulfinamide anhydride from anthranilic acid 4 and demethylated to anhydrosibiromycinone (19).

Sibiromycin (1)[1], along with anthramycin[2] and tomaymycin[3] comprise the pyrrolo(1,4)benzodiazepine antitumor antibiotics[4], a new class of natural products from actinomycetes. They are structurally related to dextrochrysin[5] and to the simpler (1,4)benzodiazepine antibiotics, neothramycins A and B[6], also from actinomycetes, and to cyclopenin and cyclopenol[7], Penecillium metabolites. Of the pyrrolo(1,4)benzodiazepine antibiotics, only sibiromycin is a glycoside and only sibiromycin contains the doubly unsaturated (aromatic) pyrrole ring.

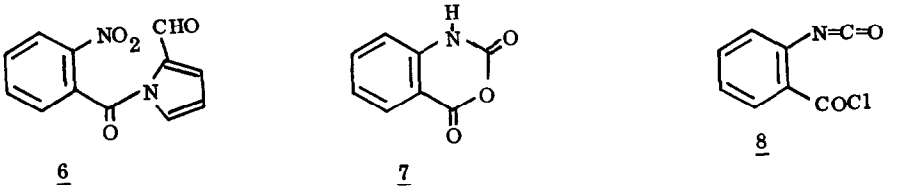


Sibiromycin (1)

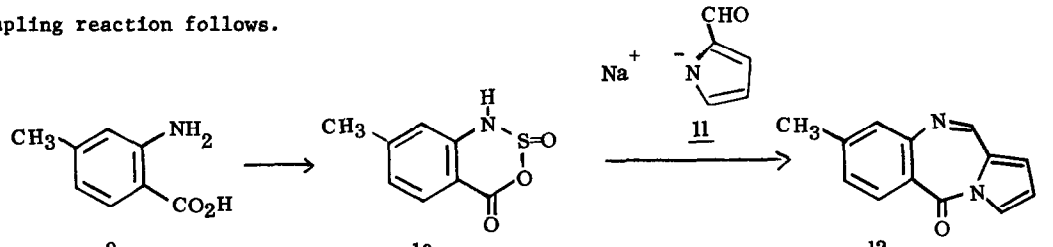
The potent biological activity of sibiromycin and its unique structural features make it a challenging target for synthesis. We chose dimethylsibiromycinone (2) or dimethylanhydrosibiromycinone (3) as our initial goal and we sought a method of forming the 1,4-benzodiazepin-5-one ring system directly[8] (i.e. in the correct oxidation state) by the condensation of a derivative of the required anthranilic acid 4 and the pyrrole aldehyde 5.



Initial studies on condensation procedures were carried out on model systems. Several attempts to effect reductive cyclization of the nitro aldehyde 6 gave compounds which were not identifiable. Condensation of pyrrole-2-carboxaldehyde or its sodium salt with isatoic anhydride (7) or isocyanate 8, afforded products of undetermined structure.



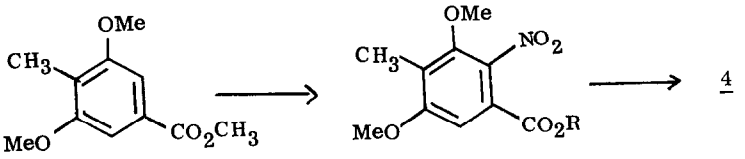
A high yield of pyrrolobenzodiazepine 12 was obtained, however, when the sodium salt of pyrrole-2-carboxaldehyde (11) was added to sulfinamide anhydride 10.[9] A procedure for this new coupling reaction follows.



A solution of 756 mg (5.01 mmoles) of anthranilic acid 9 and 2.2 ml of $SOCl_2$ in 25 ml of benzene was stirred at reflux for 2 hrs. Excess $SOCl_2$ and benzene were removed by distillation. A solution of the sodium salt, 11, prepared from 507 mg (5.34 mmoles) of pyrrole-2-carboxaldehyde and 256 mg (5.3 mmoles) of NaH (50% suspension) in 3 ml of THF, was added to the residue. The reaction mixture was stirred at room temperature for 12 hr. and concentrated. The residue crystallized from acetone/water to afford 969 mg (91%) of bright yellow crystals, mp 199-200°; IR ($CHCl_3$): 1670, 1620, and 1600 cm^{-1}; NMR ($CDCl_3$) δ=8.40 (s, 2H), 8.20 (m, 1H), 7.60 (m, 2H), 7.00 (d of d, J=4 and 2 Hz, 1H), 6.65 (t, J=4 Hz, 1H), and 2.45 ppm (s, 3H); m/e=210 (M^+).

In order to prepare dimethylanhydrosibiromycinone (3) by this coupling reaction, we needed anthranilic acid 4 and pyrrole aldehyde 5. Short, high-yield routes to these compounds are shown.

Mononitration of ester 13[10] followed by hydrolysis and reduction gave anthranilic acid 4, mp 175-177° (lit[1a] 178°), a known degradation product of sibiromycin.



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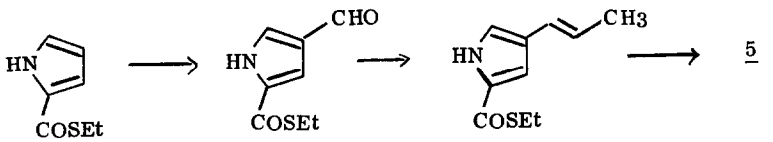
14 R=CH_3
15 R=H

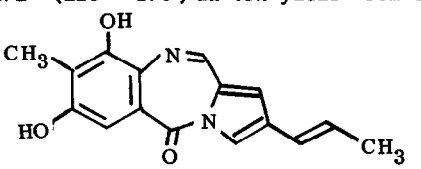
Aldehyde 5 was prepared in three steps from the known thioester 16[11]. Formylation at the 4-position gave aldehyde 17[11] which was subjected to the Schlosser modification of the Wittig reaction[12] to give the substituted thioester 18. Reductive desulfurization with deactivated W-2 Raney nickel[13] could be effected in the presence of the unsaturated side-chain when only partial conversion was attempted. Thus, stirring 390 mg (2.00 mmoles) of thioester 18 with 5.6 g of Raney nickel in 30 ml of refluxing aqueous acetone (4:1 acetone:H_2O) for 8 minutes gave a mixture of aldehyde and thioester. Chromatography on silica gel with chloroform afforded 128 mg (44%) of aldehyde 5, mp 113-115° (lit[1a] 115-116°); 164 mg (43%) of thioester was recovered.



16 17 18

When the sulfinamide anhydride coupling procedure was applied to anthranilic acid 4 and pyrrole aldehyde 5, dimethylanhydrosibiromycinone (3), mp 176-178° (lit[1a] 192-193°, authentic sample[14] 185-186°) was obtained in 67% yield.[15] Recrystallization (twice from acetone/H_2O and once from hexane) gave material with mp 183-184°; when mixed with authentic material, the melting point of synthetic 3 was not depressed. Infrared and nmr spectra of 3 were identical to those of a sample of dimethylanhydrosibiromycinone derived from sibiromycin.[14]

Treatment of dimethylanhydrosibiromycinone (3) with BBr_3 in CH_2Cl_2 at 0° afforded anhydrosibiromycinone 19, mp 270-271° (lit[1a] 270°) in 65% yield from chloroform.



19

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14. We are grateful to Professor L. H. Hurley for a sample of dimethylanhydrosibinomycinone obtained from the degradation of sibiromycin.

15. Isolation was best effected in this case by extracting an ether solution of the reaction mixture with aqueous HCl and precipitating the yellow product by adding solid Na_2CO_3 to the aqueous wash. Material obtained this way was essentially pure.

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