Conclusions

These data further establish that rotamers of acyclic carbohydrate derivatives that involve an eclipsed 1,3 interaction between substituents are energetically disfavored, a situation that is generally alleviated by rotation about an internal carbon–carbon bond to a different, gauche rotamer (sickle form). The short (three carbon) chains are more prone to populate more than one conformational state to a substantial extent, whereas prolongation of the chain tends to cause the molecule to favor one conformation more exclusively, this being the most extended arrangement compatible with avoidance of 1,3 interactions.

It is suggested that application of the Karplus equation, to quantitative determinations of dihedral angles on rotamer populations, from data obtainable by present methods, is less likely to advance the understanding of conformational behavior of polysubstituted, acyclic chains in solution than a conservative, qualitative treatment, at least until experimental methods of greater finesse are developed.

Registry No. —**1**, 7770-63-0; **2**, 34297-73-9; **3**, 34297-74-0; **4**, 16346-56-8; **5**, 34297-75-1; **6**, 34297-76-2; **7**, 34290-22-7; **8**, 34297-77-3; **9**, 34297-78-4-**10**, 7599-11-3; **11**, 34288-31-8; **12**, 6631-64-7.

A Convenient Synthesis of Myosmine

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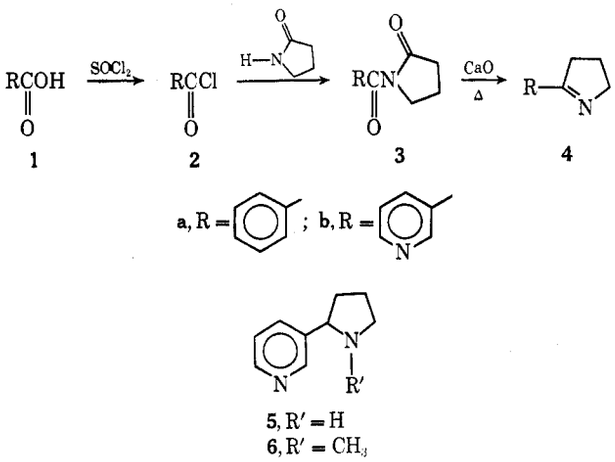
A three-step synthesis of myosmine, one of the pyrrolidine alkaloids found in various *Nicotiana species*, is described.

Myosmine (**4b**) is one of the tobacco alkaloids, and its structure has been elucidated by degradation[2] and spectral methods.[3] It has been previously synthesized by other research groups.[2b,4] We wish now to report a convenient three-step synthesis of this alkaloid (Scheme I).

The envisioned synthesis required, as the critical step, the pyrolysis of *N*-nicotinoyl-2-pyrrolidone (**3b**). Because of the wealth of data available for 2-phenylpyrroline (**4a**),[5] this proved to be a useful model for the initial evaluation of synthetic procedures. The reaction of benzoyl chloride with 2-pyrrolidone yielded the expected product, *N*-benzoyl-2-pyrrolidone (**3a**). Pyrolysis of an equal weight mixture of **3a** and calcium oxide resulted in a crude distillate, shown to be primarily 2-pyrrolidone.[6] However, the simplicity of the procedure more than compensated for the low yield of **4a** and encouraged us to apply the method, without trying to maximize yields, to the synthesis of myosmine.

Nicotinoyl chloride (**2b**) was prepared by treating nicotinic acid with an excess of thionyl chloride. Acylation of 2-pyrrolidone with **2b** afforded **3b**, which when subjected to the conditions of pyrolysis resulted in a crude product mixture which contained 67% **4b** and 33% 2-pyrrolidone.[7] The identity of **4b** was confirmed by analysis of its nmr spectrum, mass spectrum,[8] and the melting point of the picrate derivative.[4] The reported conversion of myosmine to nornicotine (**5**) and nicotine (**6**)[8] thus realizes a simple synthesis of the tobacco alkaloids.

SCHEME I
SYNTHESIS OF MYOSMINE



Experimental Section[9]

N-**Benzoyl-2-pyrrolidone** (**3a**).—A solution of 2-pyrrolidone (85.1 g) and pyridine (158 g) was added to 140 g of benzoyl chloride. After 3 days at room temperature, the pyridine was removed and the residue was suspended in benzene. This solution was washed with water, dried, and concentrated. The crude product was crystallized from hot ethanol to give 81.2 g (56%) of **3a**, mp 91° (lit.[5] mp 92°).

2-Phenylpyrroline (**4a**).—The general procedure for carrying out the pyrolysis involved intimately mixing **3a** with an equal weight of calcium oxide and placing the reactants in a distilling flask. After being heated with a free flame, the crude product mixture was collected and purified. The melting point (35–39°, lit.[5] mp 44°) and the melting point of the picrate derivative (198°, lit.[5] mp 198°), buttressed by nmr, ir, and uv spectral data, confirmed the identity of the product from this sequence.

(1) Undergraduate research participant during the summer of 1970 (NSF Grant GY 7358).

(2) (a) E. Späth, A. Wenusch, and E. Zajic, *Ber.*, **69**, 393 (1936); (b) C. F. Woodward and A. Eisner, *J. Amer. Chem. Soc.*, **66**, 911 (1944).

(3) B. Witkop, *ibid.*, **76**, 5597 (1954).

(4) E. Späth and L. Mamoli, *Ber.*, **69**, 757 (1936).

(5) F. Korte and H.-J. Schulze-Steiner, *Chem. Ber.*, **95**, 2444 (1962).

(6) We have not thoroughly investigated the mechanistic course of this reaction. However, we have noted considerable reductive cleavage occurring, finding benzene, toluene, and trimethylamine in low yields in the reaction products. The yield of **4a** was generally in the order of 15–20%, as much as 85% 2-pyrrolidone having been observed in the reaction product.

(7) This constitutes a 65% yield of **4b**, based on **3b**.

(8) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 2926 (1965).

(9) The boiling points and melting points are uncorrected.

N-**Nicotinoyl-2-pyrrolidone (3b).**—Nicotinoyl chloride hydrochloride, prepared from 20 g of nicotinic acid and 40 g of thionyl chloride, was dissolved in 10 g of pyridine and was stirred at room temperature for 1 hr. After this time, 40 g of 2-pyrrolidone was slowly added to the reaction flask and the mixture was stirred for ~15 hr at room temperature. The reaction mixture was dissolved in methylene chloride and was washed with dilute hydrochloric acid. The aqueous solution was adjusted to pH 9 and extracted with methylene chloride. After the mixture dried, the solvent was removed and the crude solid was crystallized from chloroform–hexane. The crystalline product (25.5 g, 73%) exhibited mp 104–105° (lit.[5] mp 103°).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.78; H, 5.03; N, 14.82.

Myosmine (4b).—*N*-Nicotinoyl-2-pyrrolidone (1.5 g) was mixed with an equal weight of calcium oxide, and the mixture was subjected to free-flame distillation. The crude product from this procedure (1.3 g) was shown by glc analysis (6-ft column of 2% OV-17) to be 67% myosmine and 33% 2-pyrrolidone.[10] Distillation of the crude product yielded myosmine [0.75 g 65%)], bp 82–86° (0.5 mm) [lit.[4] mp 82–84° (0.5 mm)]. This material was shown by glc to be uncontaminated with 2-pyrrolidone. Myosmine was characterized by its mass spectrum,[8] and a dipicrate derivative (mp 184–185, lit.[4] mp 184–185°). The nmr spectrum was consistant with the structure.

Registry No.—**3b**, 34236-73-2; **4b**, 532-12-7.

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(10) Other possible reaction products which might constitute the remainder of the crude product were not found from this glc analysis; only the two reported products were noted, in the ratio of 67:33.

LL-D253α, -β, and -γ, Novel Chromanones from the Fungus *Phoma Pigmentivora*

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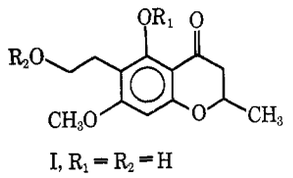
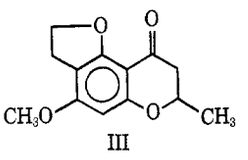
The fungus *Phoma pigmentivora* elaborates (2*R*)-5-hydroxy-6-(2′-hydroxyethyl)-7-methoxy-2-methylchromanone (LL-D253α, I) in good yield in both surface and agitated fermentations. In surface fermentation, the culture also produces in lower yield the monoacetate of this material or (2*R*)-5-hydroxy-6-(2′-acetoxyethyl)-7-methoxy-2-methylchromanone (LL-D253β, II). Treatment of the major metabolite with concentrated sulfuric acid gives 7-methoxy-5,6-(2′,3′-dihydrofuro)-2-methylchromanone (LL-D253γ, III) which is also produced in low yield in agitated fermentations of the fungus. The basic degradation of these chromanones is discussed.

In our quest for novel metabolites of pharmacological interest, we investigated the fungus *Phoma pigmentivora* or Lederle culture D253. Culture D253 was grown both by the surface and deep fermentation methods which are described in the Experimental Section. The still fermentation process in the presence of beechwood shavings[1] yielded the metabolites LL-D253α and LL-D253β which are represented respectively by structures I and II.

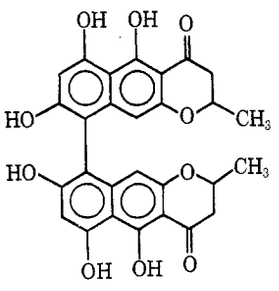




III

I, $R_1 = R_2 = H$
II, $R_1 = H$; $R_2 = CH_3CO$
IV, $R_1 = R_2 = CH_3CO$
V, $R_1 = CH_3$; $R_2 = H$
VI, $R_1 = CH_3CO$; $R_2 = H$

Agitated fermentations of the fungus yielded I as the major product and LL-D253γ or III. These metabolites are 2-methylchromanones and on tlc give a characteristic yellow spot when sprayed with sulfuric acid and heated for 1 min or so. To our knowledge, only two microbial metabolites have been isolated so far which have been characterized as chromanones. Allport and Bu'Lock isolated 5-hydroxy-2-methylchromanone from the ascomycete *Daldinia concentrica*.[2] This natural product was optically inactive. The other chromanone, rosellinic acid, was isolated from culture filtrates of *Rosellinia necatrix Berlese*[3] and shown to be 6-carboxy-8-hydroxy-2-methylchromanone.[4] A yellow pigment called cephalochromin[5] has been briefly reported. This material is a dimer in which the 2-methylchromanone nucleus is fused to an aryl group as shown below.



cephalochromin

The major metabolite I melts at 188–189°, is optically active, and has the empirical formula $C_{13}H_{16}O_5$. A uv maximum of the material in methanol at 287 nm is shifted to 325 nm in basic solution in addition to displaying a large hyperchromic effect. The ir spectrum shows a carbonyl frequency at 1655 cm^{-1} which is shifted to 1699 cm^{-1} in the diacetate IV. All of these features point to a chelated phenolic ketone.

The nmr spectrum of the monomethyl ether V was

(1) F. Kavanagh, A. Hervey, and W. J. Robbins, *Proc. Nat. Acad. Sci.*, **37**, 570 (1951).
(2) D. C. Allport and J. D. Bu'Lock, *J. Chem. Soc.*, 654 (1960).
(3) Y. Chen, *Agr. Biol. Chem.*, **24**, 372 (1960).
(4) Y. Chen, *ibid.*, **28**, 431 (1964).
(5) G. Tertzakina, R. H. Haskins, G. P. Slater, and L. R. Nesbitt, *Proc. Chem. Soc.*, 195 (1964).