[s, 3, CH_3C–N(imino)], 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.71 (s, 3, $COOCH_3$), 5.12 (m, 1, C=CH), and 5.72 (broad s, 1, C=CHCOOR); mass spectrum (70 eV) m/e M^+ 293.

Anal. Calcd for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65; N, 4.77. Found: C, 73.42; H, 10.46; N, 4.89.

Reduction of 9 and 10 with Cobaltous Bromide–Sodium Borohydride.—An alternate method of reduction of the mixture of azido mesylates (**9** and **10**) was also investigated. The reducing agent[7] was first prepared as follows: 146 mg (0.67 mmol) of anhydrous cobaltous bromide was dissolved in 10 ml of absolute ethanol (blue solution) and 312 mg (2 mmol) of dipyridyl was added (orange solution). To this solution at 0° under argon was added 76 mg (2 mmol) of sodium borohydride (blue-black solution). In a second flask, 35 mg (0.085 mmol) of a mixture of azido mesylates **9** and **10** was dissolved in 0.8 ml of dry ethanol at 0° under argon and to this solution was added dropwise 0.7 ml of the reducing solution. After 0.5 hr, the solution was poured into ether and water, and the organic phase was washed to neutrality (saturated sodium chloride) and dried ($MgSO_4$). The residue was applied to one 20 × 20 cm silica gel plate (0.5 mm thickness) and developed with a benzene–methanol–diethylamine system (94:5.4:0.6); 7 mg (R_f 0.29) of aziridines **1** and **4** was recovered. However, some saturation of the α,β-unsaturated ester function also occurred (to the extent of about 25%).

Ring Opening of 12 with Lithium Azide–Acetic Acid.—The epoxide **12** (100 mg, 0.36 mmol), lithium azide (175 mg, 3.6 mmol), and acetic acid (0.10 ml, 1.8 mmol) were stirred together in 4 ml of dry hexamethylphosphoramide for 6 days at room temperature under argon. Hexane–ether (95:5) and water were added and the phases were separated; the organic phase was washed to neutrality (saturated NaCl) and dried ($MgSO_4$) and the solvent was removed. The crude residue was applied to one 20 × 20 cm preparative silica gel plate (1.3 mm thickness) and developed twice with 20% ethyl acetate in hexane. The upper product band (R_f 0.38, 19 mg) was shown to be **14** and the lower band (R_f 0.30, 46 mg) the position isomer **13**. In addition, 5 mg of starting material **12** was recovered.

Isomer **13** had ir (CCl_4) 3630, 3590, 3520 (m, OH), 2110 (N_3), 1725 (ester C=O), 1655 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.23 [s, 6, $(CH_3)_2COH$], 1.27 (t, 3, J = 7 Hz, CH_3CH_2O–), 1.63 (broad s, 3, CH_3C=C), 2.17 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.12 (d of d, 1, HCN$_3$), 4.17 (q, 2, J = 7 Hz, $-CH_2O-$), 5.20 (m, 1, C=CH), and 5.70 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{17}H_{29}N_3O_3$: C, 63.13; H, 9.04; N, 12.99. Found: C, 63.31; H, 9.12; N, 12.92.

Isomer **14** had ir (CCl_4) 3590 (OH), 2110 (N_3), 1725 (ester C=O), and 1650 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.30 [s, 6, $(CH_3)_2CN_3$], 1.63 (broad s, 3, CH_3C=C), 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.35 (m, 1, HCOH), 4.18 (q, 2, J = 7 Hz, $-CH_2O-$), 5.20 (m, 1, C=CH), and 5.71 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{17}H_{29}N_3O_3$: C, 63.13; H, 9.04; N, 12.99. Found: C, 63.04; H, 8.94; N, 13.10.

On treatment of the two isomers separately with acetic anhydride–pyridine at room temperature for 6 hr, the top band (*i.e.*, **14**) gave an acetate [ir (CCl_4) 1740 cm^{-1} (acetate C=O); nmr ($CDCl_3$) δ 2.13 (s, 3, CH_3COO)] while the lower band gave only recovered starting material **13** (*via* infrared).

Ring Opening of 2 and 11.—Synthetic juvenile hormone **2**[4] (60 mg, 0.20 mmol), lithium azide (350 mg, 7.2 mmol), and glacial acetic acid (0.20 ml, 3.6 mmol) were dissolved in 4 ml of dry hexamethylphosphoramide and stirred under argon for 7 days at room temperature. Pentane–ether (95:5) and water were then added, and the organic phase was washed with 2 M sodium carbonate and saturated sodium chloride, dried ($MgSO_4$), and evaporated. The residue was placed on one 20 × 20 cm silica gel plate (1.3 mm PF) and developed with 12% ethyl acetate in hexane three times. In this manner two products were isolated: **3** (14 mg, 20% yield) and the position isomer **15** (40 mg, 59% yield). Azido alcohol **3** was identical with the faster eluting isomer obtained above from reduction of azido ketone **7**. Isomer **15** was completely characterized: ir (CCl_4) 3630, 3590, 3520 (broad multiplet, OH), 2110 (N_3), 1725 (ester C=O), and 1655 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.93 (t, 3, J = 7 Hz, CH_3CH_2–), 0.98 (t, 3, J = 7 Hz, CH_3CH_2), 1.15 (s, 3, CH_3COH), 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.22 (d of d, 1, HCN$_3$), 3.72 (s, 3, $COOCH_3$), 5.15 (m, 1, C=CH), and 5.72 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{18}H_{31}N_3O_3$: C, 64.06; H, 9.26; N, 12.45. Found: C, 64.29; H, 9.12; N, 12.30.

Similarly, the all-trans isomer **11**[4] (53 mg, 0.18 mmol), lithium azide (350 mg, 7.2 mmol), and glacial acetic acid (0.20 ml, 3.6 mmol) were dissolved in 4 ml of dry hexamethylphosphoramide and stirred for 9 days. Work-up as above gave a residue which was applied to one 20 × 20 cm silica gel plate (1.3 mm PF) and developed eight times with 10% ethyl acetate in hexane. Again, two bands were recovered and identified. The upper band was shown to be identical with that of the azido alcohol **8** (10 mg, 17% yield) and the lower band (25 mg, 41% yield) was shown to be that of the position isomer **16**: ir (CCl_4) 3630, 3590, 3530 (broad multiplet, OH), 2110 (N_3), 1730 (ester C=O), and 1655 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.93 (t, 3, J = 7 Hz, CH_3CH_2–), 0.98 (t, 3, J = 7 Hz, CH_3CH_2–), 1.18 (s, 3, CH_3COH), 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.18 (d of d, 1, HCN$_3$), 3.72 (s, 3, $COOCH_3$), 5.16 (m, 1, C=CH), and 5.71 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{18}H_{31}N_3O_3$: C, 64.06; H, 9.26; N, 12.45. Found: C, 64.22; H, 9.10; N, 12.20.

***trans*-2-Azidocyclohexanol.**—To 3.9 g (0.08 mol) of lithium azide and 2.3 ml (0.04 mol) of glacial acetic acid in 20 ml of hexamethylphosphoramide was added 2.0 g (0.02 mol) of cyclohexane oxide and the milky suspension was stirred at room temperature for 4 days. Pentane–ether (95:5) and 2 M sodium carbonate were added, the layers were separated, and the organic phase was washed to neutrality. After drying ($MgSO_4$), the solvent was removed and the residue was distilled, bp 95° (0.5 mm). This product (both prior to and after distillation) was homogeneous on three vpc columns (2 m 3% OV-225, 98°; 4 m 20% UCON 90M, 170°; 2 m 3% PDEAS, 100°) and was identical in all respects with a sample of *trans*-2-azidocyclohexanol prepared as described,[10] with sodium azide in hot aqueous dioxane.

Registry No.—**1**, 33780-87-9; **3**, 33780-88-0; **4**, 33780-89-1; **7**, 33780-90-4; **8**, 33780-91-5; **9**, 33780-92-6; **10**, 33886-27-0; **13**, 33886-28-1; **14**, 33780-93-7; **15**, 33780-94-8; **16**, 33780-95-9; *trans*-2-azidocyclohexanol, 10027-78-8.

The Synthesis of *trans*-3′-Methylnicotine[1a]

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Recently Rueppel and Rapoport reported that *dl*-1,3-dimethylpyrrolinium-3-$^{14}CH_3$ chloride (**1**) is incorporated into 3′-methylnicotine (**2**) by *Nicotiana glutinosa*.[2] The asymmetric center at C-2′ was assigned the *S* configuration on the basis of ORD and CD studies. However, the configuration at C-3′ remained unassigned. The superimposition of the nmr spectrum of *dl-trans*-3′-methylnicotine, synthesized in the present study, with the nmr spectrum of the biosynthesis product[3] establishes the absolute stereochemistry of the biosynthesis product as 2′*S*,3′*S* (**2a**). The nmr spectrum of **2a** displays in addition to the assignable signals for the NCH_3, CCH_3, and aromatic protons, a series of signals between δ 2.6 and 1.4 ppm integrating for five protons and a multiplet centered near δ 3.2 ppm integrating for one proton. The nmr spectrum of

(1) (a) Presented in part at the 162nd Meeting of the American Chemical Society, Washington, D. C., Sept 1971. (b) NDEA Predoctoral Fellow and American Foundation for Pharmaceutical Education Fellow.

(2) M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, **92**, 5528 (1970).

(3) The authors are indebted to Professor Henry Rapoport for providing the nmr spectrum of the biosynthesis product.

nicotine (**3**) also displays a multiplet centered near δ 3.2 ppm which however represents two protons.[4] In order to achieve a more thorough understanding of these nmr characteristics, a complete nmr assignment for *trans*-3′-methylnicotine has been carried out (Table I) *via* model deuteration and pseudocontact shift reagent studies.

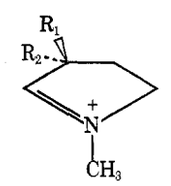
TABLE I
CHEMICAL SHIFTS AND RELATIVE CONTACT SHIFTS FOR **2a** COORDINATED WITH Eu(DPM)$_3$[a]

Proton	δ, ppm	$\Delta\delta$, ppm[b]
H_a	2.55 (d, J = 8 Hz)	1.9
H_b	2.0 (m)[c]	1.7
H_c	2.26 (m)	0.6
H_d	1.32 (m)	0.6
H_e	2.41 (m)	0.6
H_f	3.18 (m)	0.6
CCH_3	0.96 (d, J = 7 Hz)	0.9
NCH_3	2.07 (s)	1.2
$H_{a'}$	8.41 (m)	10.0
$H_{b'}$	7.60 (m)	2.8
$H_{c'}$	7.15 (m)	3.1
$H_{d'}$	8.41 (m)	7.9

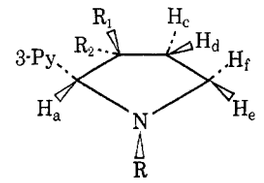
[a] Spectra were recorded at 100 MHz in CCl_4 at 0, 20, 27, 35, and 55 mol % Eu(DPM)$_3$ with TMS as internal standard. [b] Relative contact shifts calculated from the four Eu(DPM)$_3$ spectra and normalized to give a value of 10.0 for the largest proton shift ($H_{a'}$). [c] Calculated from relative contact shift value.

As part of our synthetic studies on analogs of nicotine,[5] we have prepared 1-hydroxy-2-(3-pyridyl)-3,3-dimethylpyrrolidine (**4**).[6] The nmr spectrum of **4** shows two singlets for the *gem*-dimethyl groups at δ 1.12 and 0.62 ppm. The high-field signal was assigned to the methyl group cis to the pyridine ring since it should be shifted upfield due to the shielding effect of the aromatic π cloud. We have observed similar field effects in the *trans*- and *cis*-1-cyclohexyl-4-methoxycarbonyl-5-aryl-2-pyrrolidinones (**5a** and **5b**, respectively) in which the signals for the methoxycarbonyl methyl groups of the trans compounds occur near δ 3.7 ppm, 0.5 ppm downfield relative to the corresponding cis compounds.[7] Based on the above considerations and the fact that the *C*-methyl group doublet of **2** centers at δ 0.96 ppm near the *trans*-methyl group of **4**, we decided to prepare the trans isomer **2a** as the more likely candidate for the biosynthetic product.

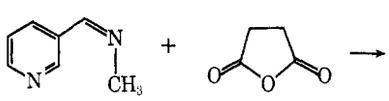
The synthesis of **2a** was achieved according to the following reaction sequence. Paralleling our previous studies,[8] the condensation of *N*-3-pyridylidenemethylamine (**6**) and succinic anhydride gave *trans*-1-methyl-5-(3-pyridyl)-2-pyrrolidinone (**7**). As previously observed[8] the coupling constant for the C-5 methine proton doublet was 5 Hz as expected for the trans configuration. Attempted lithium aluminum hydride reduction of **7** to the hydroxymethylpyrrolidine **8** in ether or tetrahydrofuran was accompanied by partial reduction of the pyridine ring. However, the corresponding methyl ester **9** was smoothly converted to **8** by lithium aluminum hydride. Confirmation of the 4,5 trans stereochemistry was obtained from the nmr of the methyl ester **9** since the methoxycarbonyl methyl signal appeared at δ 3.75 ppm, whereas the corresponding signal in the cis ester would be expected to occur near δ 3.2 ppm.[7,8] Subsequent reduction of the tosylate **10** with lithium aluminum hydride yielded *trans*-3′-methylnicotine (**2a**). The high-resolution mass and



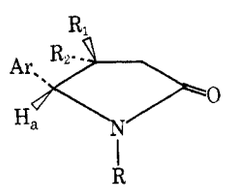
1a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$



2a, $R = R_1 = CH_3$; $R_2 = H_b$
b, $R = R_2 = CH_3$; $R_1 = H_b$
3, $R = CH_3$; $R_1 = R_2 = H$
4, $R = OH$; $R_1 = R_2 = CH_3$
8, $R = CH_3$; $R_1 = CH_2OH$; $R_2 = H_b$
10, $R = CH_3$; $R_1 = p\text{-}CH_2OTs$; $R_2 = H_b$



6



5a, R = cyclohexyl; $R_1 = COOCH_3$; $R_2 = H$
b, R = cyclohexyl; $R_1 = H$; $R_2 = COOCH_3$
7, $R = CH_3$; Ar = 3-pyridyl; $R_1 = COOH$; $R_2 = H$
9, $R = CH_3$; Ar = 3-pyridyl; $R_1 = COOCH_3$; $R_2 = H$
11, $R = CH_3$; Ar = 3-pyridyl; $R_1 = R_2 = H$

nmr spectra were consistent with the reported spectra.[2] Thus it is possible to assign the relative stereochemistry of **2** as trans and, based on the reported ORD and CD curves,[2] the absolute stereochemistry of the biosynthetic product as 2′*S*,3′*S*. Assuming that the enzymatic processes responsible for the formation of **2a** do not involve inversion at the asymmetric center of **1**, it may be concluded that (3*S*)-1,3-dimethyl-1-pyrrolinium chloride (**1a**) and not the 3*R* enantiomer (**1b**) is selectively incorporated into **2a** by *Nicotiana glutinosa*.

At 100 MHz, the δ 3.2 ppm region of the nmr spectrum of **2a** (Figure 1a) integrates for one proton and appears similar to the corresponding region in the spectrum of nicotine which, however, integrates for two protons. The spectrum of 5′,5′-dideuterionicotine (structure **3** in which H_e and H_f are replaced by deuterium atoms), prepared by $LiAlD_4$ reduction[9] of cotinine[10] **11**, shows a one-proton triplet at δ 3.04 ppm (J = 8 Hz) which clearly can be assigned to H_a. Consequently, the second low-field signal in the nicotine spectrum must be due to one of the two C-5′ protons, presumably H_f, which would be expected to appear

(4) M. Ohashi, I. Morishima, and T. Yonezawa, *Bull. Chem. Soc. Jap.*, **44**, 576 (1971).
(5) N. Castagnoli, Jr., A. P. Melikian, and V. Rosnati, *J. Pharm. Sci.*, **58**, 860 (1969).
(6) N. Castagnoli, Jr., and A. P. Melikian, unpublished results.
(7) M. Cushman and N. Castagnoli, Jr., *J. Org. Chem.*, **36**, 3404 (1971).
(8) N. Castagnoli, Jr., *ibid.*, **34**, 3187 (1969).
(9) A. M. Duffied, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 2926 (1965).
(10) E. R. Bowman and H. McKennis, *Biochem. Prep.*, **10**, 36 (1963).

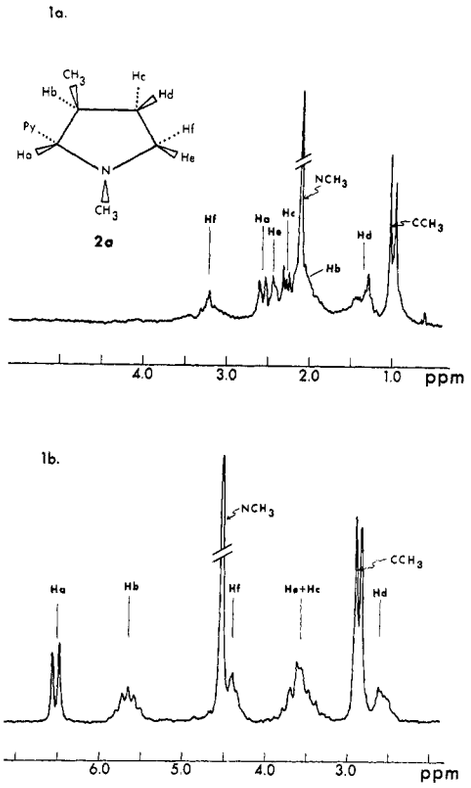


Figure 1.—(a) 100-MHz nmr spectrum of **2a** in CCl_4. (b) 100-MHz nmr spectrum of **2a** in CCl_4 complexed with 55 mol % Eu(DPM)$_3$.

downfield relative to H_e.[11] Based on these observations, the δ 3.2 ppm multiplet in the spectrum of **2a** must also be assigned to H_f. The partially resolved doublet at δ 2.55 ppm (J = 8 Hz) can therefore tentatively be assigned to H_a.

Confirmation of these assignments was obtained with the aid of the pseudocontact shift reagent tris(dipivalomethanato)europium [Eu(DPM)$_3$].[12] At a concentration of 55 mol % Eu(DPM)$_3$, the signals for the nonaromatic protons of **2a** (Figure 1b) are well separated except for two overlapping multiplets centered at δ 3.6 ppm. As was recently observed with nicotine,[4] the europium coordinates with the pyridine and not the pyrrolidine nitrogen of **2a** since the relative contact shifts of the aromatic proton signals are much greater than the corresponding shifts of the nonaromatic proton signals (Table I). On the basis of geometry, one would predict that the signal for H_a should be shifted downfield to a greater extent than the remaining pyrrolidine proton signals of **2a**, a prediction consistent with the assignment of H_a to the doublet at δ 2.55 ppm. The proton which should be next most deshielded is H_b which appears in Figure 1b as the multiplet at δ 5.66 ppm. Knowing the chemical shift of this multiplet at various concentrations of Eu(DPM)$_3$, it was possible to extrapolate to zero concentration and locate this signal at δ 2.0 ppm, overlapping with the signal for the *N*-methyl group (Figure 1a). In a similar way, the signals centered at δ 4.42 and 2.63 ppm (Figure 1b) were shown to correspond to the multiplets at δ 3.18 and 1.32 ppm, respectively, while the two-proton multiplet at δ 3.6 ppm (Figure 1b) must correspond to the multiplets at δ 2.41 and 2.26 ppm (Figure 1a). The assignments for these signals are indicated in Figure 1 and Table I. It is of interest to note that the signals for H_a and H_d occur at higher fields than in nicotine due to the shielding effect of the *cis*-methyl group. The observed shielding effect of the methyl group in **2a** of about 0.5 ppm is consistent with methyl group shielding effects observed in other five-membered ring systems.[13]

(11) The observed difference in chemical shift values between H_e and H_f in the nmr spectrum of nicotine implies that the *N*-methyl group assumes a preferred configuration trans to the pyridine ring: I. R. Simpson, J. C. Craig, and W. D. Kumler, *J. Pharm. Sci.*, **56**, 708 (1967); S. Ohki and M. Yoshino, *Chem. Pharm. Bull.*, **16**, 269 (1968). The contribution of the deshielding effect of the nitrogen lone pair on H_f [M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.* **86**, 3364 (1964)] relative to the shielding effect of the *N*-methyl group on H_e [J. B. Lambert and R. G. Keske, *Tetrahedron Lett.*, **No. 25**, 2023 (1969)] to this difference in chemical shift remains unresolved.

(12) J. K. M. Sanders and O. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971).

Experimental Section[14]

***N*-3-Pyridylidenemethylamine** (6).—A solution of CH_3NH_2 (33.37 g, 1.07 mol) and pyridine-3-carboxaldehyde (107.11 g, 1.00 mol) in C_6H_6 (200 ml) containing molecular sieves (75 g) was stirred for 12 hr at room temperature. The residue obtained after filtering and removing the solvent was distilled to give a colorless oil (110.39 g, 92%): bp 37° (0.2 mm); nmr δ 8.84 (m), 8.60 (m), 8.02 (m), 7.27 (m, aromatic signals), 8.24 (q, J = 1.5 Hz, N=CH), 3.88 ppm (d, J = 1.5 Hz, CH_3).

Anal. Calcd for $C_7H_8N_2$: C, 69.97; H, 6.71; N, 23.31. Found: C, 70.01; H, 6.85; N, 23.48.

***trans*-1-Methyl-4-carboxy-5-(3-pyridyl)-2-pyrrolidinone** (7).—The above Schiff base (91.10 g, 0.76 mol) and succinic anhydride (75.85 g, 0.76 mol) were refluxed in xylene (100 ml) for 24 hr. After cooling, the xylene was decanted from the reaction mixture and the remaining brownish oil dissolved in 5% $NaHCO_3$ (800 ml). The resulting solution was washed with $CHCl_3$ (two 800-ml portions), decolorized with activated carbon (3 g), and warmed on a steam cone to remove traces of $CHCl_3$. The pH of the solution was adjusted to 4.7 with H_3PO_4 to precipitate the product (58.62 g, mp 192–194°). An additional crop (33.51 g, mp 187–192°) was obtained after concentrating the filtrate to 225 ml. The combined material (92.13 g, 55%) was crystallized from EtOH (1700 ml) to give the analytical sample: mp 194–194.5°; nmr ($CDCl_3$–Py-d_5, 1:1) δ 14.0 (s, OH), 8.62 (m), 7.63 (m), 7.34 (m) (aromatic signals), 4.95 (d, J = 5 Hz, H_a), 2.95 (m, $CHCH_2$), 2.69 ppm (s, CH_3).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.71; H, 5.31; N, 12.92.

***trans*-1-Methyl-4-methoxycarbonyl-5-(3-pyridyl)-2-pyrrolidinone** (9).—A solution of **7** (13.85 g, 0.063 mol) in 2 *N* methanolic H_2SO_4 (110 ml) containing molecular sieves (5.0 g) was stirred for 16 hr at room temperature. The filtered solution was added slowly to 8% $NaHCO_3$ (250 ml) and the resulting mixture extracted with $CHCl_3$ (four 200-ml portions). Evaporation of the dried ($MgSO_4$) extracts yielded a clear, light amber oil (13.78 g, 93%) which gave colorless needles (11.94 g, 81%) from Et_2O–Me_2CO (75 + 15 ml): mp 83–84°; nmr δ 8.63 (m), 7.64 (m), (m) (aromatic signals), 4.86 (d, J = 5 Hz, H_a), 3.75 (s, OCH_3), 2.92 (m, $CHCH_2$), 2.69 ppm (s, NCH_3).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.74; H, 5.79; N, 11.96.

***trans*-3′-Hydroxymethylnicotine** (8).—The trans ester **9** (6.00 g, 25.6 mmol) was stirred in a solution of $LiAlH_4$ (3.64 g, 96.0 mmol) in Et_2O (350 ml) for 24 hr at room temperature. The reaction mixture was decomposed by the addition of H_2O (3.5 ml), 15% NaOH (3.5 ml), and finally H_2O (11.0 ml). The suspension was filtered, the filtrate dried ($MgSO_4$), and after removing the solvent the gold-colored residue (3.52 g, 72%) was distilled (short path) to yield an almost colorless oil: bp 87° (10 μ);

(13) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon, Oxford, 1969, pp 236, 237.

(14) All reactions were performed under a nitrogen atmosphere and solvents were concentrated on a rotary evaporator under vacuum. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nmr spectra were recorded on a JEOL 100-MHz instrument and, except where noted, in $CDCl_3$ solvent with TMS as internal standard. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

nmr δ 8.41 (m), 7.76 (m), 7.21 (m) (aromatic signals), 5.15 (b, OH), 3.56 (d, J = 5 Hz, CH_2O), 2.92 (d, J = 8 Hz, H_a), 2.11 (s, CH_3), 3.19 (m, H_f), 2.00 ppm (m, 4 H).

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.72; H, 8.17; N, 14.46.

trans-**3′-Methylnicotine** (**2a**).—The above hydroxymethyl compound **8** (1.81 g, 9.41 mmol) in pyridine (40 ml) was treated with tosyl chloride (1.79 g, 9.40 mmol) at 1° for 21 hr. The solution was then added to ice-cold 5% K_2CO_3 (100 ml) and the mixture extracted rapidly with $CHCl_3$ (four 200-ml portions). After drying ($MgSO_4$), the $CHCl_3$ and pyridine were removed *in vacuo* to yield a reddish-brown oil (3.70 g) which was dissolved in Et_2O (200 ml) and treated with $LiAlH_4$ (0.35 g, 9.4 mmol) at room temperature for 12 hr. The reaction mixture was decomposed with H_2O (0.35 ml), 15% NaOH (0.35 ml), and finally H_2O (1.05 ml). After filtering, drying ($MgSO_4$), and removing solvent, the residue (1.59 g) was chromatographed on alumina. Elution with $CHCl_3$ gave the 3′-methylnicotine (**2a**) (0.88 g, 53%) which was purified by short-path distillation: bp 40–42° (1.0 mm). The homogeneity of the distillate was established by observing only one peak on glpc (retention time 245 sec, 1/8 in. × 6 ft, 3% OV 17 on acid-washed Chromosorb W, 100–120 mesh, 146° column temperature, N_2 flow 26 ml/min).

Mass spectrum. Calcd for $C_{11}H_{16}N_2$: m/e 176.1313. Found: 176.1299. Calcd for $C_6H_{12}N$ (1,3-dimethyl-1-pyrrolinium fragment): 98.0970. Found: 98.0966. Mass fragments: m/e 176 (43), 175 (14), 134 (100), 119 (14), 98 (86).

The dipicrate was prepared for analysis, mp 199–200°.

Anal. Calcd for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.47; H, 3.48; N, 17.54.

Registry No.—**2a**, 33223-98-2; **2a** dipicrate, 33223-99-3; **6**, 16273-54-4; **7**, 33224-01-0; **8**, 33224-02-1; **9**, 33224-03-2.

Ferrocenophanes. An Improved Synthesis of 3-Phenyl[5]ferrocenophane-1,5-dione Involving a Reverse Aldol Condensation[1]

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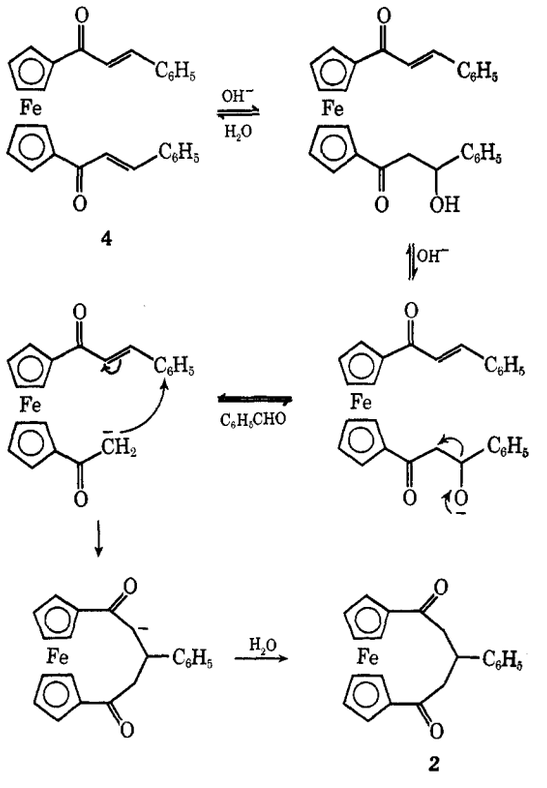
It has been reported[2] that 1,1′-diacetylferrocene (**1**) and benzaldehyde undergo an alkali-catalyzed aldol type condensation to form mono- and dibenzaldehyde derivatives and a yellow product. One of several suggested structures for the yellow product was 3-phenyl-[5]ferrocenophane-1,5-dione (**2**). This structure was later confirmed by Furdik, *et al.*[3] Barr and Watts[4] have synthesized **2** from acetylferrocene by first preparing 1-acetyl-1′-cinnamoylferrocene (**3**) (80% yield) and then by cyclizing the product under alkaline conditions to **2** (69% yield). This results in an overall yield of 55% for the two reactions.

We have recently synthesized **2** in two steps starting with ferrocene. Ferrocene is first dicinnamoylated by the Friedel–Crafts reaction to yield 1,1′-dicinnamoylferrocene (**4**), which is treated with base to yield **2**. The overall yield for the two steps was 73%. This yield is considerably higher than the previously reported yield of 55% and starts with the readily available ferrocene rather than acetylferrocene.

Nielson and Houlihan[5] discussed a number of important syntheses involving a Michael condensation followed by an intramolecular aldol condensation. The synthesis of **2** appears to be a unique example of a reverse aldol condensation step in a synthesis followed by an intramolecular Michael addition. A probable mechanism for this synthesis involves a base-catalyzed reverse aldol type condensation (reverse Claisen–Schmidt) to form the carbanion which is followed by internal Michael addition to form the heteroannular bridge (Scheme I).

SCHEME I



Since **4** is a symmetrical molecule, base attack on either cinnamoyl group leads to the carbanion intermediate after a reverse aldol condensation. In the case of base treatment of **3**, attack on the acetyl group generates the necessary carbanion for ring closure to yield **2**. However, if the cinnamoyl group is attacked, a reverse aldol condensation would lead to the carbanion of **1** which would not lead to the product. This could account for the smaller yield starting with **3**.

Experimental Section

Infrared spectra were recorded as Nujol mulls on a Beckman IR-4 and were calibrated against polystyrene film; nmr spectra were determined in deuteriochloroform on a Varian A-60 using TMS as an internal standard. Analyses were performed at Huffman Laboratories, Inc., Wheatridge, Colo. All melting points were determined using a Reichert Austria melting point apparatus and are uncorrected.

(1) The views expressed herein are those of the author and do not necessarily reflect the views of the United States Air Force or the Department of Defense.

(2) T. A. Mashburn, Jr., C. E. Cain, and C. R. Hauser, *J. Org. Chem.*, **25**, 1982 (1960).

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