give a mobile yellow oil (2.0 g) which solidified on standing. The crude solid was recrystd from petr ether (bp 40–60°) to yield a white powder (1.2 g; 40.2%), mp 94–96°. *Anal.* ($C_{14}H_{19}ClN_2$) C, H, N.

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Structure of Hydroxycotinine, a Nicotine Metabolite†

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In an attempt to establish the structure of hydroxycotinine, a mammalian metabolite of nicotine isolated from the urine of smokers, the syntheses of both diastereomeric 3-hydroxycotinines were undertaken. Two independent routes led to the same 3-hydroxycotinine which upon epimerization gave metabolic hydroxycotinine. Mass spectral and nmr analyses of these diastereomers and also deuterated model compounds established the structure of metabolic hydroxycotinine to be *trans*-1-methyl-3-(*R*)-hydroxy-5-(*S*)-3-pyridyl-2-pyrrolidinone.

The major metabolic pathways of the tobacco alkaloid nicotine (**1**) in the mammalian species studied involve a series of oxidations of the pyrrolidine ring[1] to produce in general more polar and pharmacologically less active[2] compounds than the parent substance. The γ-lactam cotinine (**2**) is the principal metabolite of nicotine and has been reported to be further metabolized to a hydroxylated product which has been tentatively assigned the structure 3-hydroxycotinine[3] (**3**). McKennis, *et al.*, have reported the isolation of hydroxycotinine from smoker's urine[3] and also from the urine of dogs,[4] rats,[5] and humans[6] treated with cotinine. Others have observed this metabolite in tissue incubates of nicotine and cotinine.[7] Elemental analysis and ir data suggested the presence of a hydroxylactam system. Conversion of the metabolite to optically active cotinine of known absolute configuration established that the asymmetric center at C-2′ of nicotine is unaltered and suggested that the newly introduced OH function is located either at C-3 or C-4 of the pyrrolidinone ring. The preparation of metabolic hydroxycotinine as a minor product obtained from the diazotization of a 3-aminocotinine led McKennis to propose 3-hydroxycotinine as the structure of the metabolite.[3] However, because of the ease with which aliphatic diazo compounds undergo rearrangement,[8] the authors noted that this assignment must be considered tentative. No attempt was made to establish the configuration of the metabolite at C-3.

As part of our studies on the mechanisms of oxidative metabolism of N-containing compounds,[9] we have undertaken an analysis of the metabolism of cotinine. In order to obtain an authentic sample of metabolic hydroxycotinine, (*S*)-cotinine (2), prepared by oxidation of (*S*)-nicotine,[10] was administered iv to a 4-kg male rhesus monkey and the organic soluble base fraction isolated from the 48-hr urine. The material corresponding to hydroxycotinine was purified by preparative tlc or alumina column chromatography

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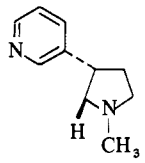
and had a mp and ir spectrum corresponding to that reported for the metabolite. The high-resolution mass and 100-MHz nmr spectra of this metabolite support the proposed 3-hydroxylactam structure. Mass fragments at *m/e* 174 (loss of H_2O) and *m/e* 114 (loss of pyridyl radical) correspond to species **4** and **5**, respectively. The nmr spectrum shows 2 overlapping multiplets centered near 4.7 ppm which can be assigned to the signals for **Ha** and **Hd** and a 2-H^+ multiplet centered at 2.5 ppm due to the signals for protons **Hb** and **Hc** (*cf.* structure **3**). In order to confirm these speculations and to investigate the stereochemistry of metabolic hydroxycotinine, the syntheses of *cis*- and *trans*-3-hydroxycotinine, **3a** and **3b**, respectively, were undertaken.



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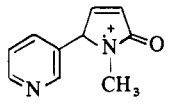

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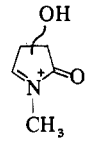

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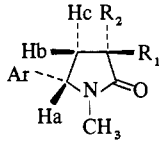
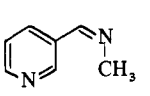


2, Ar = 3-pyridyl; $R_1 = R_2 = H$
3a, Ar = 3-pyridyl; R_1 = Hd; R_2 = OH
3b, Ar = 3-pyridyl; R_1 = OH; R_2 = Hd
16a, Ar = C_6H_5; R_1 = Hd; R_2 = OH
16b, Ar = C_6H_5; R_1 = OH; R_2 = Hd
20a, Ar = 3-pyridyl; R_1 = Hd; $R_2 = OSO_2CH_3$
20b, Ar = 3-pyridyl; $R_1 = OSO_2CH_3$; R_2 = Hd
21a, Ar = 3-pyridyl; R_1 = Hd; $R_2 = OCOCH_3$
21b, Ar = 3-pyridyl; $R_1 = OCOCH_3$; R_2 = Hd
25a, Ar = C_6H_5; R_1 = Hd; $R_2 = OCOCH_3$

Our first approach to the synthesis of **3** proceeded by way of the pyrrolinone (**8**) which is readily obtained by the condensation of pyridylidenemethylamine (**6**) with diethyl oxalacetate (**7**).[11,12] Attempted conversion of **8** to the potentially reducible dione **9** by base hydrolysis and decarboxylation proved unsuccessful, a result not inconsistent with literature reports on related systems.[13] The acid-catalyzed hydrolysis of **8** appeared more encouraging since a crude hydrochloride could be isolated which gave an nmr spectrum suggestive of the dione structure. However, the free base proved to be unstable, presumably undergoing self-condensation.[11,12] The conversion of **8** to **3** was achieved in moderate yields either by treating the acid hydrolysis reaction mixture with $NaBH_4$ or by a hydrolysis-decarboxylation-reduction sequence affected by HI in acetic acid containing NaH_2PO_2.[11] In both instances exclusively 1 of the 2 possible diastereomeric 3-hydroxycotinines was isolated. As will be established later, this isomer of mp 149°, which will be referred to as synthetic hydroxycotinine, is the C-3 epimer of metabolic hydroxycotinine.

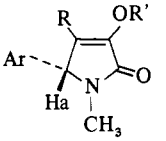
The nmr spectrum of synthetic hydroxycotinine differs from that of metabolic hydroxycotinine principally in that the signals for the CH_2's, **Hb** and **Hc**, occur as separate multiplets centered at 1.8 and 2.9 ppm instead of the overlapping multiplet at 2.5 ppm observed for the metabolite. The signal for the NCH_3 group appears at 2.64 ppm, 0.19 ppm upfield relative to the position of the corresponding signal for metabolic hydroxycotinine. This separation of the NCH_3 signals allowed us to conclude that the crude product isolated from these reactions contained less than 10% of the isomer corresponding to metabolic hydroxycotinine. Similarly, even though tlc and glpc did not affect any separation of the synthetic and metabolic hydroxycotinines, the nmr spectra of the crude metabolic hydroxycotinine isolates indicated that none of the isomer represented by our synthetic 3-hydroxycotinine was present in the monkey urine extracts.



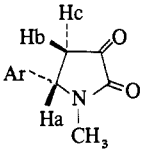
6

$EtO_2CCOCH_2CO_2Et$

7

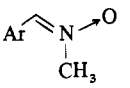


8, Ar = 3-pyridyl; R = COOEt; R' = H
23, Ar = C_6H_5; R = COOEt; R' = H
24, Ar = C_6H_5; R = Hb; R' = $COCH_3$

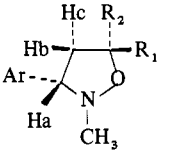


9, Ar = 3-pyridyl
22, Ar = C_6H_5

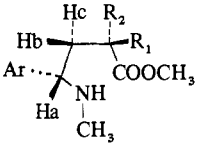
A second approach to the synthesis of **3** was based on the reported hydrogenolysis of 5-alkoxycarbonylisoxazolidines to α-hydroxy-γ-amino esters, which spontaneously cyclize to 3-hydroxy-2-pyrrolidinones.[14] The required isoxazolidine, **11**, was synthesized *via* the condensation of α-3-pyridyl-*N*-methylnitrone (**10**) and methyl acrylate. The stereochemistry of the previously reported isoxazolidines had not been established. Since the hydrogenolysis of **11** to the hydroxyamino ester **12** should proceed with retention of configuration at C-3 and C-5, the stereochemistry of the resulting pyrrolidinone, **3**, should follow directly from the stereochemistry of **11**. Therefore, it was important to attempt to isolate both the *trans*- and *cis*-isoxazolidines **11a** and **11b** and, if possible, to assign the relative stereochemistry at C-3 and C-5.



10, Ar = 3-pyridyl
18, Ar = C_6H_5



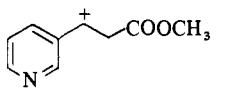
11a, Ar = 3-pyridyl; R = $COOCH_3$; R_2 = Hd
11b, Ar = 3-pyridyl; R_1 = Hd; $R_2 = COOCH_3$
17a, Ar = C_6H_5; $R_1 = COOCH_3$; R_2 = Hd
17b, Ar = C_6H_5; R_1 = Hd; $R_2 = COOCH_3$



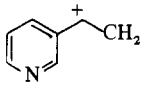
12a, R_1 = Hd; R_2 = OH
12b, R_1 = OH; R_2 = Hd

Nmr analysis of the crude reaction product suggested the presence of isomeric isoxazolidines since three sharp singlets assignable to NCH_3 resonances in the ratio of 8:1:1 were observed. Preparative tlc led to the isolation of the major and one minor product in pure form while the second minor component could be obtained in only partially pure form. High-resolution mass spectral analysis of the pure minor fraction gave the expected parent ion corresponding to $C_{11}H_{14}N_2O_3$ with a major fragment at *m/e* 163, while the mass spectrum of the more abundant component gave the

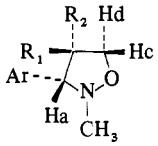
same parent ion with a major fragment at *m/e* 105. From the mass spectral data, these 2 compounds appeared to be positional isomers with the minor component bearing the MeO_2C group at C-4, structure **13a** or **13b**, and undergoing fragmentation to produce species **14** (*m/e* 163) while the major component, **11a** or **11b**, fragments to produce species **15** (*m/e* 105). The mass spectrum of **11** shows no ion at *m/e* 163 and similarly the spectrum of **13** shows no ion at *m/e* 105.



14
m/e 163



15
m/e 105



13a, Ar = 3-pyridyl; $R_1 = COOCH_3$; R_2 = Hb
13b, Ar = 3-pyridyl; R_1 = Hb; $R_2 = COOCH_3$
19a, Ar = C_6H_5; $R_1 = COOCH_3$; R_2 = Hb
19b, Ar = C_6H_5; R_1 = Hb; $R_2 = COOCH_3$

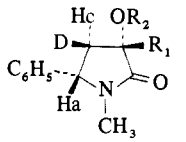
Nmr analysis of the minor product confirmed structure **13**. The signals for CH_2, **Hc** and **Hd**, appear as a doublet (4.25 ppm), as does the signal for **Ha** (3.83 ppm). Irradiation of the quartet assignable to the signal for **Hb** (3.37 ppm) causes both doublets to collapse to singlets. On the basis of previous studies with related 5-membered ring systems,[15] this molecule can be assigned the trans configuration since the singlet for the CO_2CH_3 resonance occurs at 3.7 ppm, whereas the corresponding signal for the cis isomer would be expected upfield near 3.2 ppm due to the shielding effect of the vicinal aromatic group. The second minor isomer, which could be obtained as a 2:1 mixture with the major component, has been assigned the *cis*-4-methoxycarbonylisoxazolidine structure, **13b**, since the CO_2CH_3 signal appears, as expected, at 3.2 ppm.

Confirmation that the major product from the nitrone–Me acrylate condensation was the desired 5-methoxycarbonyl isomer, **11**, was obtained by nmr. Particularly definitive were the presence of a 1-proton quartet centered at 4.70 and a 1-proton triplet centered near 3.80, corresponding to the signals for **Hd** and **Ha**, respectively. As required, the signal for the CO_2CH_3 group occurs at 3.8 ppm. All attempts to detect the epimeric 5-methoxycarbonylisoxazolidine failed.§ Hydrogenolysis of **11** yielded exclusively the previously obtained 149° melting 3-hydroxycotinine. Evidence presented below allows us to assign the stereochemistry of this hydroxycotinine as cis (**3a**) and hence we can also assign the stereochemistry of **11** as trans (**11a**).

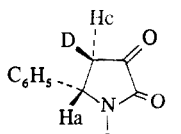
In order to prepare the elusive epimeric 3-hydroxycotinine, epimerization at C-3 of the readily available isomer of mp 149° was achieved by treating the mesylate, **20**, with NaOAc in AcOH. The ir and nmr spectra of the resulting acetoxy compound **21** were identical in all respects with those of the acetate of metabolic hydroxycotinine. Hydrolysis of this epimerized acetoxy derivative yielded racemic metabolic hydroxycotinine. Repeating the above sequence but starting with metabolic hydroxycotinine gave synthetic acetoxycotinine, thus confirming the C-3 location of the OH function in the metabolite.

Having established the location of the OH function as C-3, it remained to determine the stereochemistry of metabolic hydroxycotinine. The sequence designed to accomplish this stereochemical assignment necessitated the use of the Ph analog **16** of synthetic hydroxycotinine.# Compound **16** was obtained by reduction of the corresponding isoxazolidine **17**§ or by reductive decarboxylation of the pyrrolinone **23**. The stereochemistry of **16** was readily shown to be the same as that of synthetic hydroxycotinine since, except for the aromatic proton signals, the nmr spectra of these two compounds were essentially identical. Most importantly, the signals for CH_2, **Hb** and **Hc**, appear as separate multiplets centered at 1.8 and 2.9 ppm, characteristic for the synthetic hydroxycotinine series of compounds.

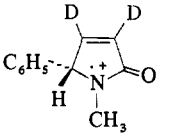
Chromic acid oxidation of **16** yielded the stable 1-methyl-5-phenyl-2,3-pyrrolidinedione (**22**) which was readily converted to the enol acetate **24**. Catalytic hydrogenation of **24** would be expected to proceed with cis addition of H_2 and furthermore to yield predominantly the *cis*-acetoxypyrrolidinone **25a**. Reduction of **24** gave exclusively the acetoxy compound corresponding to the synthetic series, strongly suggesting that synthetic 3-hydroxycotinine bears the 3 and 5 substituents in a cis relationship, **3a**, in which case the metabolite is the corresponding trans compound, **3b**. More definitive stereochemical evidence was obtained with the aid of the D reduction product **26**. That the D had added cis was apparent from the mass spectrum of **26** which showed the expected D enrichment of the parent ion and also in the fragment **27** generated by loss of AcOH. Thermal eliminations of this type are known to proceed in a cis fashion[16] and therefore **Hc** must be cis to OAc and the D atoms must also be cis as depicted in **26**. It remained to be established whether **Ha** was cis or trans to **Hc**. Hydrolysis of **26** gave **28** which was then oxidized to the dione **29**. The nmr spectrum of **22** shows a quartet for **Ha** at 4.93 ppm, while the signals for protons **Hb** and **Hc** appear as quartets at 3.25 and 2.57 ppm being coupled both geminally (J = 19 Hz) and vicinally to **Ha**. The quartet at 2.57 ppm can be assigned to **Hc**, since **Hc**, shielded by the *cis*-Ph, should appear upfield relative to **Hb**. The vicinal coupling constants of 3.5 Hz (J_{ac}) and 8 Hz (J_{ab}) for trans and cis coupling, respectively, are also consistent with reported values in 5-membered lactam systems.[15] In the spectrum of the deuterated pyrrolidinedione **29**, the signal at 3.3 ppm due to **Hb** is absent and the signals for **Ha** (4.9 ppm) and **Hc** (2.6 ppm) appear as doublets, J_{ac} = 3.5 Hz. This spectrum requires the D atom in **29** to be cis to **Ha** and working back-



26, R_1 = D, $R_2 = COCH_3$
28, $R_1 = R_2$ = H



29



27

§For reasons which will become apparent, the phenyl analog 16 of synthetic 3-hydroxycotinine was synthesized by reduction of the corresponding 5-methoxycarbonylisoxazolidines, 17. Once again only one of the two possible 5-methoxycarbonylisoxazolidines, 17a and 17b, was obtained together with smaller amounts of both 4-methoxycarbonyl compounds, 19a and 19b.

#This sequence of reactions involves the pyrrolidinedione 22. Presumably because of its basic character attempted preparation of the corresponding pyridine compound 9 failed.

wards, the structure of the catalytic deuteration product of the enol acetate **24** must be **26** and possess the anticipated 3,5-cis stereochemistry. Therefore the Ph analog of synthetic hydroxycotinine must be **16a** and synthetic hydroxycotinine must be **3a**, while metabolic hydroxycotinine must be *trans*-1-methyl-3-hydroxy-5-(3-pyridyl)-2-pyrrolidinone. Since the absolute stereochemistry of metabolic hydroxycotinine at C-5 has been shown to be the same as that established for nicotine,[3] the absolute stereochemistry of metabolic hydroxycotinine can now be assigned as 3-*R* and 5-*S* as drawn in **3b**. Studies designed to further our understanding of the mechanism of this stereospecific metabolic oxidation currently are being pursued.

Experimental Section**

Isolation of Metabolic Hydroxycotinine from Monkey Urine. (*S*)-Cotinine[10] (**2**, 2.0 g) dissolved in 50 ml of saline was administered to a 4-kg male rhesus monkey by iv infusion over an 8-hr period. The total 48-hr urine (pH 9) was extd continuously with $CHCl_3$ for 40 hr. Silica gel tlc (EtOH–Me_2CO–C_6H_6–concd NH_4OH, 5:40:50:5) of the $CHCl_3$ residue (1.3 g) indicated 5 major fluorescent spots with R_f values 0.20, 0.38, 0.45, 0.51, 0.67. The band corresponding to the R_f 0.38 spot was eluted from prep plates (2 mm) with MeOH and the resulting residue dissolved in a min vol of warm Me_2CO. After 3 weeks at 5°, large, slightly yellow crystals of metabolic hydroxycotinine (**3b**) were collected. Alternately, **3b** could be obtd by Al chromatography eluting cotinine first with CH_2Cl_2 and **3b** with 1–2% MeOH in CH_2Cl_2: mp 110–111° (lit.[6] mp 110–112°); ir 3550 cm^{-1} and 3320 (OH), 1690 (C=O) (lit.[6] 3360 cm^{-1}, 1690); nmr δ 2.5 ppm, m (**Hb**, Hc), 2.83 s (NCH_3), 4.7 m (Ha, Hd); mass spectrum, calcd for $C_{10}H_{12}N_2O_2$: 192.08986, found: 192.08995; mass fragments, *m/e* 174, 161, 114, 106, 79.

1-Methyl-3-hydroxy-4-ethoxycarbonyl-5-(3-pyridyl)-3-pyrrolin-2-one (8). A soln of 3-pyridylidenemethylamine†† (6, 12.9 g, 0.1 mole) and freshly distd diethyl oxalacetate (18.8 g, 0.1 mole) in C_6H_6 (200 ml) was heated under reflux for 15 hr. Upon cooling, a solid (12.0 g, 0.055 mole, 55%) sepd which after crystn from EtOH gave the analytical sample: mp 178–179°; ir 3430 cm^{-1} (OH), 1720 (ester C=O), 1690 (amide C=O); nmr δ 1.1 ppm t, *J* = 7 Hz (CCH_3), 3.0 s (NCH_3), 4.2 q, *J* = 7 Hz (CH_2), 5.7 ppm S (Ha). *Anal.* ($C_{13}H_{14}N_2O_4$) C, H, N.

***cis*-3-Hydroxycotinine (3a) from 8.** (a) A soln of pyrrolinone **8** (8.0 g, 30 mmoles) in 47% HI (50 ml) and HOAc (50 ml) contg $NaH_2PO_2 \cdot H_2O$ (10.0 g, 94 mmoles) was heated under reflux for 3 hr. The CO_2 produced was collected *via* an N_2 sweep as $BaCO_3$ (3.7 g, 19 mmoles, 63%). The solvent was removed and the residue dissolved in 50 ml of 5% aq $NaHCO_3$. Exhaustive extn with CH_2Cl_2 yielded crude **3a** (1.8 g, 9.4 mmoles, 31%). Recrystn from xylene gave the analytical sample: mp 148–149° (lit.[3] mp 149–151°); ir 3280 cm^{-1} and 3160 (OH), 1670 (C=O); nmr δ 2.0 ppm m (Hc), 2.64 s (CH_3), 2.9 m (**Hb**), 4.5 m (Ha, **Hd**), 5.5b exchange (OH); mass spectrum, *m/e* 192, 174, 135, 114, 106. *Anal.* ($C_{10}H_{12}N_2O_2$), C, H, N. (b) Pyrrolinone **8** (10.0 g, 38.2 mmoles) was heated under reflux for 3 hr in 2 *N* HCl. After removing the solvent, the residue in 50 ml of H_2O was stirred overnight with $NaBH_4$ (4.0 g, 100 mmoles). The reaction mixt was exhaustively extd with CH_2Cl_2 and the residue obtd (4.0 g) chromatogd on 50 g of Al. Elution with $CHCl_3$ and 0.5% MeOH–$CHCl_3$ gave 300 mg of a crystn solid (mp 130–134) which upon recrystn from Me_2CO yielded **3a**: mp 145–147, nmr, identical with **3a** obtd by method (a).

α-3-Pyridyl-*N*-methylnitrone (10). A soln of pyridine-3-carboxaldehyde (12.8 g, 120 mmoles) and *N*-methylhydroxylamine · HCl (10.0 g, 100 mmoles) in abs EtOH (100 ml) was stirred 18 hr at room temp. The solid which formed (5.6 g) was collected and combined with an addnl 2.8 g obtd by concg the mother liquors to 50 ml. The total nitrone · HCl (18.4 g, 98 mmoles, 81%) was crystd from abs EtOH and the resulting 16 g dissolved in H_2O satd with K_2CO_3. Exhaustive extn with $CHCl_3$ gave 11.2 g (82 mmoles, 69%) of the hygroscopic free base **10** which was recrystd from hexane for analysis: mp 74–76°; nmr δ 3.90 ppm s (CH_3), 7.43 s (PyCH). *Anal.* ($C_7H_8N_2O$) C, H, N.

***trans*-2-Methyl-3-(3-pyridyl-5-methoxycarbonyl)isoxazolidine (11a).** The nitrone **10** (4.9 g, 29 mmoles) was heated under reflux in Me acrylate (25.0 g, 290 mmoles) for 2 hr.‡‡ The residue obtd after removing the solvent was submitted to prep tlc (silica gel, 2 mm; Et_2O–cyclohexane, 7:3). Three bands, A, B, and C, were visualized under uv light (R_f 0.13, 0.21, 0.28, resp). The compds found in all 3 bands were eluted individually with MeOH and rechromatogd. In this way the compds of bands A and C were obtd in pure form while the material of band B remained contaminated with the material of band A. The compd isolated from band A proved to be the *trans*-5-methoxycarbonylisoxazolidine **11a**: ir (neat) 1750 cm^{-1} (C=O); nmr δ 2.66 ppm s (NCH_3), 2.8 m (**Hb**, Hc), 3.78 s (OCH_3), 3.8 t, *J* = 8 Hz (Ha), 4.6 q, *J* = 7 Hz (**Hd**); mass spectrum, calcd for $C_{11}H_{14}N_2O_3$: 222.10044, found: 222.10031; main fragments *m/e* 161, 144, 105. The compd isolated from band C proved to be *trans*-2-methyl-3-(3-pyridyl-4-methoxycarbonyl)isoxazolidine (**13a**): ir (neat) 1750 cm^{-1}; δ^{100} = 2.60 ppm s (NCH_3), 3.37 m (**Hb**), 3.70 s (OCH_3), 3.83 d, *J* = 8 Hz (Ha), 4.25 d, *J* = 7 Hz (Hc, **Hd**). Irradiation at 3.37 ppm led to the collapse of the 2 doublets to singlets appearing at 3.83 ppm (**Ha**) and 4.25 ppm (Hc, **Hd**); mass spectrum, calcd for $C_{11}H_{14}N_2O_3$: 222.10044, found: 222.10058; main fragments *m/e* 192, 163, 137. *cis*-2-Methyl-3-(3-pyridyl-4-methoxycarbonyl)isoxazolidine (**13b**) was obtd from band B as a 2:1 mixt with **11a**: nmr δ^{100} 2.63 ppm s (NCH_3), 3.20 s (OCH_3), 3.45 m (Hb), 2.38 (**Ha**, hidden under addnl lines), 4.25 d, *J* = 7 Hz (Hc, **Hd**).

***cis*-3-Hydroxycotinine (3a) from 11a.** The mixt of isoxazolidines described above (4.9 g, 22 mmoles) was hydrogenated (2 atm) in abs EtOH (100 ml) over freshly prepd Raney Ni catalyst (2.0 g) for 10 hr. The reaction mixt was filtered and the oily residue obtd chromatogd on acid-washed Al (150 g) with $CHCl_3$ (1 l.) and the product eluted with 1% MeOH in $CHCl_3$. Crystn from Me_2CO of the solid obtd gave pure **3a** (2 g, 10.4 mmoles, 47%) identical in all respects with the product obtd from the pyrrolinone reactions.

Epimerization Studies. (a) *cis*-3-Hydroxycotinine (**3a**, 192 mg, 1 mmole) in anhyd pyridine (10 ml) was treated with $MeSO_2Cl$ (340 mg, 3.0 mmoles) for 18 hr at 5°. The reaction mixt was added to ice H_2O (150 ml) and rapidly extd with $CHCl_3$. The oily mesylate (**20a**) obtd after removing the solvent displayed the following nmr: δ 2.2 ppm m (Hc), 2.76 s (NCH_3), 3.0 m (**Hb**), 4.76 t, *J* = 7 Hz (Ha), 5.43 t, *J* = 8 Hz (**Hd**). The crude mesylate was heated at reflux for 1 hr in glacial HOAc (10 ml) contg NaOAc (1 g). The reaction mixt was added to ice H_2O (50 ml) and the pH adjusted to 9 with $NaHCO_3$. Extn with $CHCl_3$ gave acetate **21b**: nmr δ 2.17 s (CCH_3), 2.5 m (Hb, Hc), 2.78 s (NCH_3), 4.76 t, *J* = 7 Hz (Ha), 5.50 t, *J* = 8 Hz (**Hd**). The nmr spectrum of the acetate obtd by treating metabolic hydroxycotinine with Ac_2O in pyridine proved to be identical with **21b**. Hydrolysis in 5% NaOH (1 hr, 80°) of the crude acetate **21b** obtd from the above epimerization reaction gave *trans*-3-hydroxycotinine (**3b**): mp 71–72°; mass spectrum, calcd for $C_{10}H_{12}N_2O_2$: 192.08986, found 192.08995. The nmr, ir spectra, and mass fragmentation pattern of **3b** were identical with metabolic hydroxycotinine. *Anal.* ($C_{10}H_{12}N_2O_2 \cdot 0.5H_2O$) C, H, N.

(b) Metabolic hydroxycotinine (40 mg, 0.2 mmole) was treated with $MeSO_2Cl$ (100 mg, 0.9 mmole) in anhyd pyridine (3 ml). Work-up as described above gave the desired mesylate **20b**: nmr δ 2.6 ppm m (Hb, Hc), 2.80 s (NCH_3), 3.33 s (OCH_3), 4.8 t, *J* = 7 Hz (Ha), 5.4 q, *J* = 6 Hz (Hd). The mesylate **20b** was heated under reflux for 1 hr in glacial HOAc (3 ml) contg NaOAc (300 mg). The resulting acetate displayed an nmr spectrum identical to the spectrum of the acetate **21a** obtained by direct acetylation of synthetic hydroxycotinine (**3a**): nmr δ 2.0 ppm m (Hc), 2.16 s (CCH_3), 3.0 m (**Hb**), 2.71 s (NCH_3), 4.55 t, *J* = 7 Hz (Ha), 5.41 t, *J* = 8 Hz (**Hd**).

***cis*-1-Methyl-3-hydroxy-5-phenyl-2-pyrrolidinone (16a). (a) From pyrrolinone 23.** Following the procedure for the synthesis of **3a**, the pyrrolinone **23**[18] (26 g, 100 mmoles) was heated under reflux for 3 hr in HOAc (100 ml) contg 47% HI (100 ml) and $NaH_2PO_2 \cdot H_2O$ (20 g, 188 mmoles). Work-up of the reaction mixt as previously described gave crude **16a** (3.1 g, 15.7 mmoles, 15.7%) which upon crystn from Me_2CO yielded the analytical sample: mp 148–149°; ir 3560 cm^{-1} and 3340 (OH), 1690 (C=O); nmr δ 2.0

**Unless otherwise specified, all reactions were performed under a N_2 atmosphere. Organic solvents were dried over anhyd $MgSO_4$ and were concd *in vacuo* by means of a rotary evaporator. Mps (Hoover-Thomas) are uncorrected. Ir spectra were taken in $CHCl_3$ on a Perkin Elmer 337 spectrophotometer; nmr spectra were taken in $CDCl_3$ (TMS) on a Varian A-60A (δ) or a JEOL 100 MHz (δ^{100}); mass spectra were taken on an AEI MS 902 (direct inlet, 70 eV). Microanalyses were performed by the Microanalytical Labs, University of California, Berkeley, Calif.

††M. S. Cushman and N. Castagnoli, Jr., unpublished results.

‡‡Evidence in the literature that product formation in related 1,3-dipolar addition reactions may be temperature dependent[17] led us to study this reaction under a variety of conditions. However, we observed essentially no variation in product distribution.

ppm m (Hb), 2.63 s (NCH_3), 2.9 m (Hc), 4.5 m (Ha, Hd), 5.45 b exchange (OH). *Anal.* ($C_{11}H_{13}NO_2$) C, H, N.

(b) From isoxazolidine 17a. A soln of α-phenyl-*N*-methylnitrone (18, 16 g, 120 mmoles) in methyl acrylate (100 ml) was heated under reflux for 2 hr. After removal of solvent, the nmr showed the presence of 3 isomeric isoxazolidines as previously observed in the prepn of the pyridine compd **11a**. The mixt of isoxazolidines was hydrogenated (2 atm) in abs EtOH (100 ml) over Raney Ni (2.0 g). Al (150 g) chromatography of the residue obtd from the redn gave with 1% MeOH–$CHCl_3$ 16a (7.0 g, 36.5 mmoles, 30%), identical with the material from 23.

1-Methyl-5-phenyl-2,3-pyrrolidinedione (22). To a cooled, stirred soln of 16a (1.0 g, 5.3 mmoles) in 40 ml of glacial HOAc was added dropwise (30 min) an ice cold soln of $Na_2Cr_2O_7 \cdot 2H_2O$ (0.8 g, 2.6 mmoles) in 20% H_2SO_4 (2.6 ml). Following an addnl 10 min at room temp, the reaction mixt was added to ice cold H_2O (350 ml) and the resulting soln extd with $CHCl_3$. Removal of the solvent gave an oil which solidified on standing. Crystn from Me_2CO–hexane gave pure 22 (0.9 g, 90%): mp 139–140°; ir 1170 cm^{-1} (ketone C=O), 1700 (lactam C=O); nmr δ = 2.57 ppm q, J_{bc} = 19 Hz, J_{ac} = 3.5 Hz (Hc), 3.00 s (NCH_3), 3.25 q, J_{bc} = 19 Hz, J_{ab} = 8 Hz (Hb), 4.93 q (Ha), 7.5 m (Ar). *Anal.* ($C_{11}H_{11}NO_2$) C, H, N.

1-Methyl-3-acetoxy-5-phenyl-3-pyrrolin-2-one (24). A soln of the dione 22 (0.44 g, 2.3 mmoles) in Ac_2O (5 ml) contg anhyd pyridine (1 ml) was maintained at 5° for 18 hr. The reaction mixt in ice H_2O (200 ml) was made basic ($NaHCO_3$) and extd with $CHCl_3$. The oil obtd was sublimed at 50° (0.01 mm) to yield pure enol acetate: mp 51–53°; nmr δ 2.30 ppm s (CCH_3), 2.83 s (NCH_3), 5.00 d, J = 2 Hz (Ha), 6.83 d, J = 2 Hz (Hb), 7.4 m (Ar). *Anal.* ($C_{13}H_{13}NO_3$) C, H, N.

***cis*-1-Methyl-3-acetoxy-5-phenyl-2-pyrrolidinone (25a).** The enol acetate **24** (0.40 g, 1.7 mmoles) in abs EtOH (10 ml) was hydrogenated (1 atm) over 10% Pd/C (100 mg) for 7 hr. The solid obtd after filtering and removing solvent was crystd from C_6H_6–hexane to yield 0.25 g (1.1 mmoles, 63%) pure **25a**: mp 110–111°; ir 1750 cm^{-1} (ester C=O), 1700 (lactam C=O); nmr δ 1.8 ppm m (Hc), 2.6 s (CCH_3), 3.0 m (Hb), 4.43 t, J = 8 Hz (Ha), 5.38 t, J = 8 Hz (Hd), 7.4 m (Ar). *Anal.* ($C_{13}H_{15}NO_3$) calcd C, 66.94; H, 6.48; N, 6.00. Found: C, 67.51; H, 6.32; N, 6.42.

1-Methyl-*cis*-(3-acetoxy-5-phenyl)-*cis*-3,4-dideuterio-2-pyrrolidinone (26). The enol acetate **24** (0.35 g, 1.5 mmoles) was hydrogenated (1 atm) in EtOAc (20 ml) with D_2 (99%) over Pd/C (100 mg) for 4 hr. Work-up gave an oil which crystd from C_6H_6–hexane to yield pure 26: mp 110–111°; ir 1750 cm^{-1} (ester C=O), 1700 (lactam C=O); nmr δ 1.80 ppm d, J = 8 Hz (Hc), 2.17 s (CCH_3), 4.40 d, J = 8 Hz (Ha), 7.4 m (Ar); mass spectrum ($C_{13}H_{13}D_2NO_3$) calcd: 235.11773, found: 235.11807, mass fragments, *m/e* 192, 175, 118, 107.

***trans*-1-Methyl-4-deuterio-5-phenyl-2,3-pyrrolidinedione (29).** A soln of 26 (200 mg, 0.84 mmole) in MeOH (5 ml) contg NaOH (100 mg) was heated under reflux for 1 hr. The nmr spectrum of the crude product 28 obtained by $CHCl_3$ extn of the hydrolysis residue showed no CH_3CO_2 signal although the C-3 D had completely exchanged during the reaction.

Oxidn of this material with $Na_2Cr_2O_7$–H_2SO_4 as previously described gave the required dione 29: mp 139–140°; ir, 1770 cm^{-1} (ketone C=O), 1700 (lactam C=O); nmr δ^{100} 2.57 ppm d, J = 3.5 Hz (Hc), 2.91 s (NCH_3), 4.95 d, J = 3.5 Hz (Ha), 7.4 m (Ar).

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(±)-6,6-Difluoronorgestrel, a New Synthetic Hormonal Steroid†

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Totally synthetic (±)-6,6-difluoronorgestrel (6) was prepared from (±)-17β-hydroxy-13β-ethyl-4-gonen-3-one (1) using the NOF and SF_4 chemistry outlined in Scheme I. The title compound was prepared to see if the potentiation of progestational activity caused individually by 6,6-difluoro and 18-methyl substitution of norethindrone could be combined into a single compound. The progestational activity of **6** was approximately the same as that of (±)-norgestrel.

We recently described[1-8] the use of NOF and SF_4 as synthetic reagents which are useful in multistep syntheses of fluorinated steroids.[9-14] An important extension of this method has now been made in going from 13β-methyl steroids formally derived from natural materials to totally synthetic (±)-6,6-difluoronorgestrel (**6**), a compound of interest because of its relationship to the potent synthetic progestational hormones,[15,16] norethindrone (**7a**),[15,16] 6,6-difluoronorethindrone (**7b**),[7,8] and norgestrel (**7c**).[17-19] Since the individual potentiating effects of 18-methyl and 6,6-difluoro substitution in 17β-hydroxy-17α-ethynyl-19-norsteroids have been established,[15,16,20,21] **6** represents a combination of these effects within a single molecule.

Because **6** and **7c** possess an angular ethyl group, it is necessary to prepare them by total synthesis. The necessary intermediate, (±)-17β-hydroxy-13β-ethyl-4-gonen-3-one (**1**) was obtained by the classical 19-norsteroid total syntheses

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