$CHCl_3$, which were washed with saturated NaCl and dried.§ Evaporation of the $CHCl_3$ left 5.5 g of oil which was chromatographed & to give 1.4 g of colored powder. This was recrystallized twice from EtOH–H_2O (Norit) to give 0.4 g (8%) of **12**: mp 141.5–143.5°; ir (CCl_4) 3190 (NH), 1665 cm^{-1} [C(=O)N]; nmr ($CDCl_3$) δ 2.63, 2.65 (overlapping s, 2, 4-CH_2), 3.79 (s, 3, OCH_3 over a broad 1-H multiplet); mass spectrum 245 (M^+), 202 (base). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.8; N, 5.7. Found: C, 73.7; H, 7.9; N, 5.6.

5-*m*-Methoxyphenyl-2-methyl-2-azabicyclo[3.3.1]nonane (5-*m*-Methoxyphenyl-2-methylmorphan) (13) Hydrobromide. Methylation of **12** according to Gassman and Fox[11] gave a 100% yield of oily **14**: ir (film) 1635 cm^{-1} [C(=O)N]; nmr ($CDCl_3$, HA-100) δ 2.62, 2.66 (overlapping s, 2 H, 4-CH_2), (s, 3, NCH_3), 3.66 (m, 1, 1-CH), 3.70 (s, 3, OCH_3); mass spectrum 259 (M^+), 216 (base).

Reduction of **14** according to Brown and Heim[12] gave 100% of oily **13**: mass spectrum 245 (M^+), 202 (base). The HBr salt (from Me_2CO–Et_2O) had mp 163–165° and was identical (melting point, mixture melting point, and mass spectrum) with authentic material.[2]

Optical Resolution of 1. *l*-Mandelic acid (8 g), 10 g of (±)-**1**, and 50 ml of Me_2CO, heated and stirred together briefly, gave 15.7 g of mandelate salts which were dissolved in 500–600 ml of boiling MeOH. Concentration of the solution to 100–150 ml gave 7.5 g of the *l*-mandelate salt of (−)-**1**, mp 220–221°,** which in boiling dilute NH_4OH gave 4.4 g (88%) of (−)-**1**: mp 153–154°; $[\alpha]^{20}D$ −12.3°.[1]

The combined Me_2CO and MeOH filtrates above were concentrated to 50–75 ml and treated with H_2O and NH_4OH, giving 5.5 g of a mixture of (+) and (±) bases. This in 150 ml of hot MeOH was treated with 4.4 g of *d*-mandelic acid giving (after cooling) 7.0 g of the *d*-mandelate salt of (+)-**1**, mp 218–220°, and, as above, 3.5 g (70%) of (+)-**1**, mp 152.5–154°, $[\alpha]^{20}D$ +11.8°.[1]

** A second recrystallization (with minor loss of material) is sometimes necessary.

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Deuterium Isotope Effects in the *in Vivo* Metabolism of Cotinine[1]

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In an attempt to further our understanding of the molecular mechanisms associated with the mammalian oxidative metabolism of foreign substances, we have investigated the deuterium isotope effect involved in the *in vivo* metabolism of the tobacco alkaloid cotinine. Mixtures of cotinine-d_0 and cotinine-3,3-d_2 in varying ratios were administered to Rhesus monkeys. Unchanged drug and several of its oxidized metabolites including *trans*-3-hydroxycotinine were isolated from the 24-hr urine collection. The deuterium contents of these isolated compounds were found to be greater than that present in the administered cotinine except for *trans*-3-hydroxycotinine which showed a substantial decrease in the deuterium to proton ratio. On the basis of these determinations the deuterium isotope effect for the 3-hydroxylation of cotinine was calculated to be between 6 and 7, indicating that carbon–hydrogen bond cleavage is likely to be involved in the rate-determining step in this metabolic conversion.

Current concepts concerning the chemical nature of the active oxygen species responsible for mammalian C-hydroxylations[2] of foreign substances remain vague although many of the biochemical and model chemical studies[3] point to an electron-deficient oxygen functionality. These oxidation reactions involve cleavage of a carbon–hydrogen bond, and therefore it can be anticipated that replacement of hydrogen with deuterium at the center undergoing hydroxylation will lead to a significant deuterium isotope effect ($k_H/k_D > 1$) in the event that rupture of the carbon–hydrogen bond is involved in the rate-determining step in the overall conversion. Deuterium isotope effects ($k_H/k_D < 2$) have been reported in a number of metabolic conversions of foreign substances.[4]

In the present communication we record the results of our deuterium isotope effect studies on the *in vivo* metabolism of cotinine [(*S*)-1-methyl-5-(3-pyridyl)-2-pyrrolidinone, **1a**], the principal mammalian metabolite of the tobacco alkaloid nicotine (**2**). Our studies[5] as well as those of others[6] have led to the structural elucidation of several urinary metabolites of cotinine including desmethylcotinine (**3a**), cotinine *N*-oxide (**4a**), *trans*-3-hydroxycotinine (**5a**), and 5-hydroxycotinine (**6a**). The stability, mass spectral characteristics, and ease of isolation of **5a** together with the stereospecificity of the conversion and the ready availability of cotinine-3,3-d_2 (**1b**)[7] provided an excellent opportunity to investigate the influence on C(3)-hydroxylation by replacing with deuterium the two protons α to the carbonyl group.

Cotinine-3,3-d_2 (**1b**) was easily obtained by deuterium exchange of cotinine† in D_2O in the presence of K_2CO_3. An nmr spectrum of **1b** shows three clean quartets for H_A (δ 6.62 ppm), H_B (δ 2.58 ppm), and H_C (δ 1.90 ppm), whereas the signal for H_A in the proton compound **1a** appears as a multiplet, presumably due to long-range coupling with protons H_D and H_E which together with H_B and H_C provide a complex series of lines between δ 2.8 and 1.7 ppm.

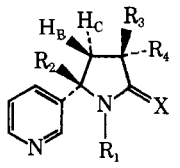
†The cotinine used in these studies was prepared by oxidation of (*S*)-nicotine[7,8] and has been shown to be enantiomerically pure (*S*)-cotinine.[9]

Table I. Selected Relative Ion Intensities of Administered (Adm) and Isolated (Isl) Cotinine-d_0 (**1a**), Cotinine-d_2 (**1b**), and Mixture A (**1a**/**1b** = 1.25/1) and Mixture B (**1a**/**1b** = 0.135/1)

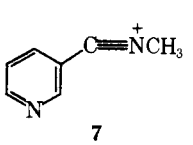
	1a		1b		Mixture A		Mixture B	
m/e	Adm	Isl	Adm	Isl	Adm	Isl	Adm	Isl
100	0.6		100	100	80	100	100	100
99	6.0	5.0	2.2	2.3	10	14	3.2	2.8
98	100	100	0.3	0.8	100	80	13.5	10.2
98/100			0.003	0.008	1.25	0.80	0.135	0.102

An electron-impact mass spectrum of cotinine shows in addition to the parent ion (M^+ 176, 32%) major fragments at *m/e* 119 (11%) for the nitrilium ion **7** and at *m/e* 98 (100%) for the pyrrolinonium ion **8**. As expected the mass spectrum of the dideuterio compound **1b** shows shifts in the parent (M^+ 178, 32%) and pyrrolinonium (*m/e* 100, 100%) ions by two mass units. An accurate determination of the deuterium incorporation in **1b** cannot be calculated from the parent ion since there is a relatively large M − 1 species (26% of the parent) due to loss of a hydrogen radical. However, the region of the base peak is exceptionally free of interfering ions and since C–D bonds are not broken in forming this fragment, isotope effects due to loss of deuterium do not occur. Thus, the ion intensities at *m/e* 100, 99, and 98 in the mass spectrum of 1 can be used to calculate the relative amounts of the d_2, d_1, and d_0 species present.

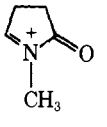
The dideuterio compound **1b** (>99% d_2 according to the above mass spectral criteria) was administered intravenously to a male Rhesus monkey, the 24-hr urine was collected, and the organic-soluble base fraction was isolated. Analytical tlc showed five fluorescent spots corresponding in R_f values to cotinine, 5-hydroxycotinine, desmethylcotinine, *trans*-3-hydroxycotinine, and cotinine *N*-oxide. The nmr and mass (Table I) spectra of the recovered cotinine isolated by preparative tlc were identical with the spectra of the administered compound, thus establishing that the starting lactam had not suffered loss of deuterium while in the animal or during work-up. Further evidence that exchange of the deuterium atoms of **1b** had not occurred came from mass spectral analysis of the metabolite, cotinine-3,3-d_2 *N*-oxide (**4b**), which was also isolated from the preparative tlc plate. The parent ion (M^+ 194, 44%) and pyrrolinonium fragment (*m/e* 100, 100%) were shifted to two mass units higher as compared with the protio metabolite. Furthermore, the corresponding relative intensities of all the major ions including the parent and base peaks for the protio and deuterio compounds were essentially identical.



	R_1	R_2	R_3	R_4	X	
1a,b	CH_3	H_A	H_D(D)	H_E(D)	O	
2a,b	CH_3	H	H	H	H_2	
3a,b	H	H	H(D)	H(D)	O	
4a,b	CH_3	H	H(D)	H(D)	O	(N→O)
5a,b	CH_3	H	OH	H(D)	O	
6a,b	CH_3	OH	H(D)	H(D)	O	



7



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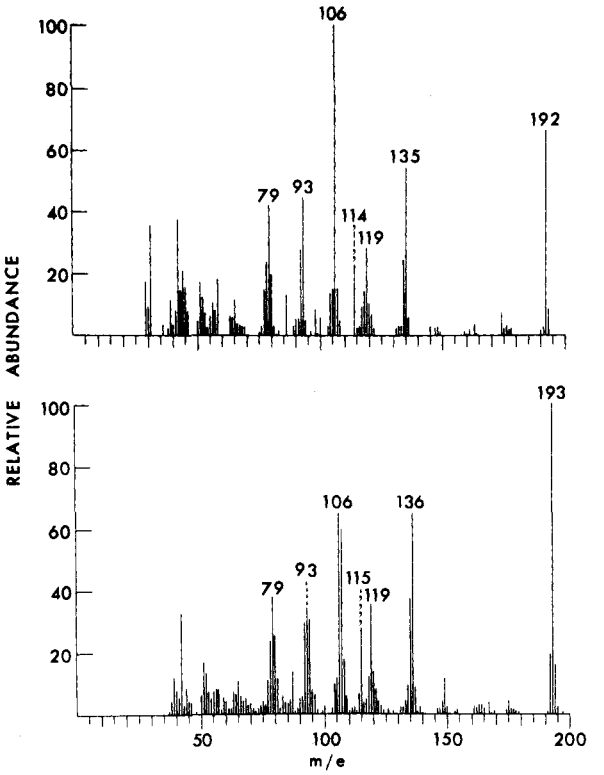


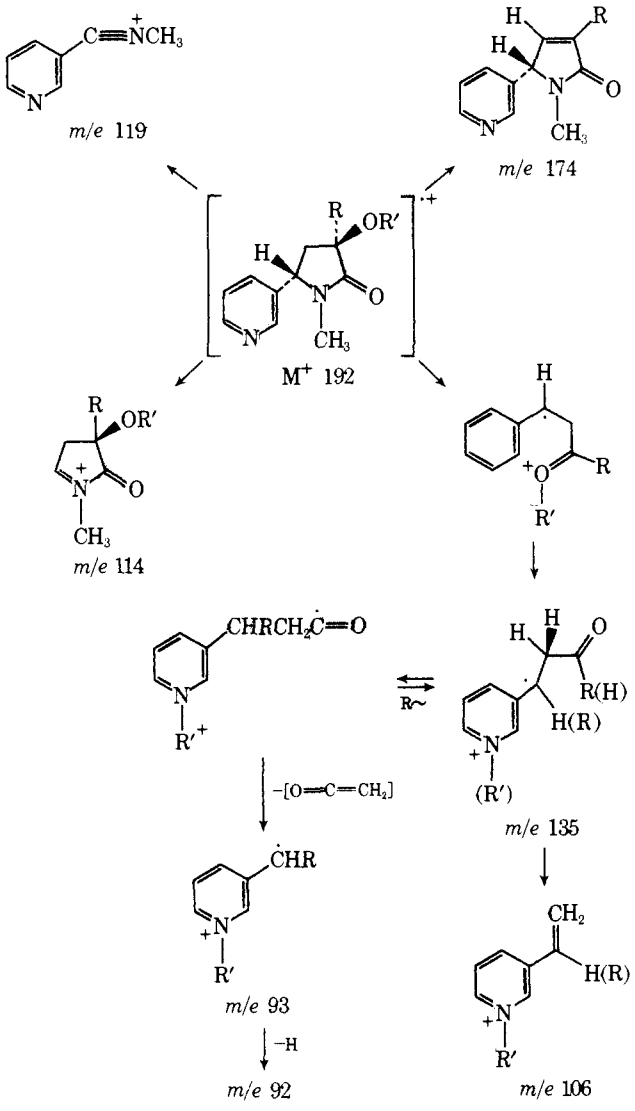
Figure 1. Mass spectra of *trans*-3-hydroxycotinines isolated from the 24-hr urine collections of a male Rhesus monkey receiving iv cotinine-d_0 (top) and cotinine-3,3-d_2 (bottom).

The mass spectrum of metabolite **5** isolated from the urine of the monkey receiving **1b** is reproduced in Figure 1 (bottom) together with the corresponding spectrum of **5** isolated after administration of **1a** (Figure 1, top). The spectrum shown in Figure 1 (top) is identical with that obtained with synthetic **5a**. The spectrum shown in Figure 1 (bottom), however, does not correspond to pure **5b** since the ion intensity at *m/e* 192 indicates that **5b** is contaminated to the extent of 15% with **5a**. Since the recovered cotinine-d_2 does not show any detectable exchange, we have assumed that the C(3)-hydroxylation of **1b** and/or the purification of **5b** is accompanied by exchange of the cis-C(3) deuterium atom.

Inspection of the mass spectra presented in Figure 1 shows that the ions corresponding to *m/e* 106, 93, and 92 in the protio compound **5a** (Fig 1a) are partially but not wholly shifted to one mass unit higher in the spectrum of compound **5** isolated after administration of cotinine-3,3-d_2 (**1b**). The intensities of these ions in the spectrum of **5b** are too great to be exclusively due to the contamination by **5a**. Furthermore, when the hydroxy proton of synthetic **5a** was labeled with deuterium, all of the above ions were completely shifted to one mass unit higher. These observations suggest that extensive ion rearrangements are occurring in the mass spectrometer. Scheme I is an attempt to rationalize the above data. A metastable scan confirms the pathway from *m/e* 135 to 106 in the protio compound **5a**.

In order to estimate the deuterium isotope effect associated with the conversion of cotinine to *trans*-3-hydroxycotinine, we administered a mixture of **1a** and **1b** shown by

Scheme I. Fragmentation Sequence Proposed to Account for the Mass Spectra of *trans*-3-Hydroxycotinine-d_0 (R = R′ = H; See Figure 1, Top) and *trans*-3-Hydroxycotinine-3-d_1 (R = D; R′ = H; See Figure 1, Bottom)



mass spectral analysis to be **1a**/**1b** = 1.25 (mixture A, Table I). Unchanged cotinine (1), cotinine *N*-oxide (4), and *trans*-3-hydroxycotinine (5) were isolated by preparative tlc and identified by mass spectrometry. It can be seen (Table I) that whereas the administered substrate (Adm) had more cotinine-d_0 than cotinine-d_2, the isolated drug (Isl) was richer in the dideuterio species showing that cotinine-d_0 is metabolized to a greater extent than cotinine-d_2. The mass spectrum of the metabolite 4 showed d_2/d_0 isotope ratio near 1 (*m/e* 192/194 = 0.9, 98/100 = 0.9). However, the mass spectrum of *trans*-3-hydroxycotinine [*m/e* 193 (20%), 192 (78), 135 (52), 134 (25), 119 (33)] showed a *m/e* 192/193 (d_0/d_1) ratio of 4/1 (Table II). Estimation of the isotope effect required the following approximate corrections: (1) 14% of the *m/e* 192 peak was subtracted from the *m/e* 193 peak to correct for the ^{13}C contribution from **5a** to the M^+ ion intensity of **5b**; (2) 4% of the *m/e* 193 peak was subtracted from the *m/e* 192 peak to correct for the $M^+ - 1$ contribution of **5b** to the M^+ of **5a**; (3) 15% of the *m/e* 193 peak was added to the *m/e* 193 peak and subtracted from the *m/e* 192 peak to correct for the assumed 15% conversion of **5b** to **5a**. Based on these approximations, the deuterium isotope effect for this conversion was calculated to be 6.2. We have assumed that further metabolic or spontaneous conversions of **5a** and **5b** proceed at similar rates and that the change in relative concentrations of **1a** and **1b** during the course of the experiment is not significant. However, the expected effects of both of these variables would decrease the experimentally determined isotope effect value and therefore any corrections would lead to an increase in the reported value.

Table II. Selected Relative Ion Intensities of *trans*-3-Hydroxycotinine-d_0 (**5a**) and *trans*-3-Hydroxycotinine-d_1 (**5b**) Isolated from the Metabolism of **1a**, **1b**, Mixture A (**1a**/**1b** = 1.25/1), and Mixture B (**1a**/**1b** = 0.135/1)

		From **1b**		From mixture A		From mixture B	
m/e	**1a**	Obsd	Cor[a]	Obsd	Cor[b]	Obsd	Cor[b]
194		16		4		7.3	
193	9	100	100	20	15	45	45
192	67	19	15	78	74	49	41
191	3			3		3	

[a]The *m/e* 192 ion intensity is corrected for the 4% M − 1 contribution of *m/e* 193. [b]The *m/e* 193 and 192 ions are corrected for 14% of the *m/e* 192 satellite at *m/e* 193, for the apparent loss of *m/e* to 192 (estimated as 15%) due to conversion of **5b** to **5a**, and the 4% M − 1 contribution of *m/e* 193 to 192.

The most significant error in the above value results from the large *m/e* 192/193 ion intensity ratio and the concomitant large ^{13}C correction factor. To avoid this problem and to check our results, we repeated the experiment using mixture B, **1a**/**1b** = 0.135 (Table I). Again, the more extensive metabolism of **1a** as compared with **1b** is evident. The composition of **1a** and **1b** decreased from 0.135 in the administered mixture of 0.102 in the isolated material (Table I). The large isotope effect for the C(3)-hydroxylation of cotinine was also confirmed. Calculations (Table II) based on the mass spectrum of **5** [*m/e* 193 (45%), 192 (49), 135 (55), 134 (22), 119 (35), 107 (43), 106 (100, 93 (46), 92 (32)] provide a k_H/k_D value of 6.7.

This unexpectedly large value represents a clearly documented primary isotope effect in the mammalian metabolism of a foreign substance. While these limited data do not permit any definitive mechanistic interpretation, it is tempting to point out the obvious analogy between this hydroxylation reaction and nonenzymatic two-electron oxidations α to a carbonyl group in which enolization is the rate-determining step.[10] In these reactions the deuterium isotope effect has been shown to be in the same range as we have observed in the metabolic formation of *trans*-3-hydroxycotinine. The fact that recovered cotinine-d_2 shows no deuterium exchange would imply that should enolization be involved, the process is either irreversible or reversible with the original deuterium atom serving as the sole proton source in the back reaction.

Experimental Section

Materials. Cotinine-3,3-d_2 (**1b**) was obtained by heating a solution of cotinine[8] [mass spectrum *m/e* 176 (32%), 175 (9), 119 (12), 118 (13), and 98 (100)] (1 g) at 100° in D_2O (>99%, 20 g) containing K_2CO_3 (1 g) for 10 days under an N_2 atmosphere. The solvent was removed under vacuum and the process repeated a second time. The final solution was extracted with 3 × 20 ml of CH_2Cl_2. The combined, dried (K_2CO_3) extracts were concentrated to yield cotinine-3,3-d_2 as an oil. The mass spectrum [*m/e* 178 (32%), 177 (10), 120 (12), 119 (17), and 100 (100)] and nmr of this oil showed the product to be essentially 100% pure. Reference samples of *trans*-3-hydroxycotinine (**5a**),[5a] cotinine *N*-oxide (**4a**),[5b] and 5-hydroxycotinine (**6a**)[5c] were available.

Animal Studies. Four experiments were carried out in which

the main variable was the nature of the cotinine used: expt 1, cotinine-d_0; expt 2, cotinine-3,3-d_2 (>99%); expt 3, mixture A (Table I); and expt 4, mixture B (Table I). The description which follows details the procedure followed for mixture B only although it applies to all studies.

A mixture containing cotinine-d_0 (**1a**, 31.2 mg) and cotinine-3,3-d_2 (**1b**, 228 mg) in 13 ml of saline was prepared and 10 ml (200 mg) were administered to a 7-kg male Rhesus monkey by iv infusion over a 10-min period. The pH of the total 24-hr urine collection was adjusted to 9 with 1 *N* NaOH and the resulting solution was extracted continuously with CH_2Cl_2 for 24 hr. Silica gel tlc (EtOH–Me_2CO–C_6H_6–concentrated NH_4OH, 5:40:50:5) of the CH_2Cl_2 residue (100 mg) indicated five major fluorescent spots with R_f values 0.17, 0.27, 0.35, 0.42, and 0.58. These correspond to cotinine *N*-oxide, *trans*-3-hydroxycotinine, desmethylcotinine, 5-hydroxycotinine, and cotinine, respectively.[11] Each band was scraped from the preparative plate and was eluted with EtOH. Mass spectra were obtained by direct insertion with an AEI MS-12 operated at a resolving power of 1000, accelerating potential 8 kV, ionizing potential 50 eV, trap current 500 μA, and source temperature 200°. Low-resolution data reduction was accomplished by a PDP 8/I computer.

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Notes

Triarylhaloethylenes as Gonadotrophin Inhibitors

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In a previous paper[1] we described the synthesis of a series of basic-ether-substituted triarylhaloethylenes as gonadotrophin inhibitors. We now wish to report the synthesis and gonadotrophin-inhibiting activity of a group of compounds related to the former but with more diversifications in structure.

Chemistry. The compounds described herein (Table I) were prepared by two general methods: (A) halogenation of the corresponding triarylethylene according to previously published[1] methods, or (B) etherification of the corresponding phenolic triarylethylene with the appropriately substituted alkyl halide in the presence of base. The yields by either method were comparable and the methods themselves were chosen on a basis of synthetic convenience relative to the availability or ease of attainment of starting materials. The synthesis of the phenanthene **8** required the preparation of 9-*p*-hydroxyphenylphenanthrene.[2] This compound was then etherified with β-diethylaminoethyl chloride (method B) and the product was chlorinated (method A) to give **8**.

All of these compounds except **7** were converted to a citrate or hydrochloride salt prior to screening. Efforts were not made to separate geometric isomers where the possibility existed; thus, in such cases, chemical characterization and biological testing were done on a mixture of isomers.

Biology. Table II indicates the gonadotrophin-inhibiting activities of these compounds as determined by the method of Holtkamp, *et al.*[3] A lower mean relative (expressed per 100 g of body weight) ventral prostate weight of the treated rats as compared with that of the controls was used as the index of pituitary gonadotrophin inhibition.

In general, these compounds were gonadotrophin inhibitory at one or more doses in the range 3–50 mg/kg/day. Compounds **1**, **4**, **6**, and **7**, however, were more active than the rest. The introduction of an additional substituent such as *p*-*tert*-butyl (**2**) or β-diethylaminoethoxy (**5**) diminished the response as did the increase in the size of the amino function to pyrrolidino (**3**). That increased coplanarity of the rings is detrimental can be seen in the lack of activity in the phenanthrene **8**.

Experimental Section

The ethylene starting material for **2** was prepared according to ref 4. Other starting materials are noted below. All melting points were taken on a Thomas-Hoover apparatus. Broad melting points, where they occurred, were attributed to mixtures of cis–trans isomers. All final products analyzed within 0.4% for C, H, and a third element (Cl or N).

***p*-(2-Chloro-1,2-diphenylvinyl)phenol.** A solution of 424 g (1.48 mol) of *p*-(1,2-diphenylvinyl)anisole[5] in CCl_4 was treated with 105 g (1.48 mol) of Cl_2 in CCl_4 over a 2-hr period. After the addition was complete, the solution was heated under reflux for 1 hr and evaporated. The oily residue was treated with petroleum ether (bp 70–90°) and the resulting solid was filtered. Recrystallization from ether gave 178 g of *p*-(2-chloro-1,2-diphenylvinyl)anisole which melted at 104–106°. Condensation of the mother liquor followed by dilution with petroleum ether gave a second crop, 156 g, mp 80–88°, and a third crop, 75 g, mp 78–86°. The total yield was 409 g (86%).

A 119-g (0.37 mol) quantity of the anisole (mp 104–106°) was added at once to 115 g (1.0 mol) of boiling (*ca.* 215°) pyridine hydrochloride. The solution was boiled for 20 min after which it was poured onto ice. The product was extracted with Et_2O to give 75