affording 32.4 g (70%) of colorless liquid, bp 46–50 °C (0.3 mmHg). This material was of sufficient purity as shown by NMR for use in the next step. ^{1}H NMR: 2.21 (t, 2), 4.42 (t, 2).

1-(($^2H_3$)-Methyl)(2,2-$^2H_3$)-1-pyrroline 1-Oxide (12). Nitro ketone 11 (15.0 g, 0.11 mol) and a solution of ammonium chloride (6.36 g) in D_2O (45 mL) were combined in a 250-mL three-necked flask fitted with a mechanical stirrer and cooled in a bath maintained at −20 °C. Zinc dust (36 g) was added in small portions over a period of 3 h such that the temperature of the reaction did not exceed 5 °C. After the addition was completed, the reaction was stirred for an additional 0.5 h at 25 °C. The mixture was filtered and the filtered cake was washed with methanol (5 × 40 mL). The combined filtrates were concentrated, and the oil was extracted with $CHCl_3$ (5 × 20 mL), dried over anhydrous $MgSO_4$, filtered, evaporated, and distilled to give 7.05 g (62%) of 12 as a white oil, bp 65–67 °C (0.3 mmHg). This material was of sufficient purity as shown by NMR for use in the next step. ^{1}H NMR: 2.08 (t, 2), 3.99 (t, 2).

5,5-Di(($^2H_3$)-methyl)(4,4-$^2H_2$)-1-pyrroline 1-Oxide (13). To a stirred solution of deuterated methylmagnesium bromide (1 M, 100 mL) in ether was added a solution of nitrone 12 (5.2 g, 50 mmol) in dry ether (50 mL) at a rate sufficient to mtaintain gentle reflux. After being stirred at 25 °C for 0.5 h, the solution was treated at 0 °C with saturated aqueous ammonium chloride (20 mL). The ether layer was decanted and combined with ether extracts (5 × 50 mL) from the aqueous layer. The solvent was evaporated to yield a yellow oil (2.89 g). To this oil were added methanol (50 mL), concentrated aqueous NH_4OH (5 mL), and copper acetate (500 mg) in the presence of a stream of air. Within 10–15 min a deep blue color developed, at which point the solution was evaporated. The blue oil was then taken up in ether (50 mL), washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, evaporated to dryness, and distilled to give 1.00 g (17%) of 13 as a white oil, bp 35–37 °C (0.03 mmHg). This material was pure by NMR. ^{1}H NMR: 2.55 (br s, 2), 6.79 (t, 1).

5,5-Di(($^2H_3$)-methyl)(2,3,3,4,4-$^2H_5$)-1-pyrroline 1-Oxide (14). A D_2O solution (10 mL) of 13 (1.00 g, 8.26 mmol) and NaOD (310 mg, 7.56 mmol) was heated at 70 °C for 12 h. The solution was evaporated to near dryness. The brown residue was extracted with $CHCl_3$ (5 × 5 mL), dried over anhydrous $MgSO_4$, filtered, evaporated, and distilled to give 900 mg (88%) of 14 as a colorless oil, which became a solid below 0 °C. This material shows only one peak by GC. Analysis by GC-MS indicated that 14 consisted of 62% of the $^2H_{11}$ species, 29% of the $^2H_{10}$, $^1H_1$ species, 6% of the $^2H_9$, $^1H_2$ species, and 1% of the $^2H_8$, $^1H_3$ species. MS: $C_6D_{11}NO$, m/e 124 (M^+).

Purification of Spin Traps. The following procedures were used to purify spin traps 9 and 14. Immediately prior to use, the spin traps (100–200 mg) were passed through a short silica gel column (1.0 g) using $CHCl_3/CH_3OH$ (100:1). The solvent was evaporated and the white oil was bulb-to-bulb distilled using a Kugelrohr apparatus (38–40 °C/0.03 mmHg) to give the spin trap as colorless oil, which became solid below 0 °C. All spin traps were stored under argon at −70 °C.

Spin Trapping of Superoxide. The superoxide-generating system consisted of xanthine (400 μM) and xanthine oxidase such that the rate of superoxide production was 10 μM/min at 25 °C. Measurement of superoxide generation was determined optically by following the reduction of cytochrome c at 550 nm, using a molar absorptivity of 20 mM^{-1} cm^{-1}. The reaction was initiated by the addition of xanthine oxidase to xanthine (400 μM) and the various spin traps (0.1 M) to a final volume of 0.25 mL. No free radical could be spin trapped if any of the components of the above reaction were not present.

Spin Trapping of Hydroxyl Radical. The spin trapping of hydroxyl radical was undertaken by the addition of ferrous sulfate (0.1 mM) to the superoxide-generating system described above.

Spin Trapping of α-Hydroxyethyl Radical. The spin trapping of α-hydroxyethyl radical was undertaken by the addition of absolute ethanol (0.28 M) to the hydroxyl radical generating system described above.

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The Product of Reserpine Autoxidation

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Oxidation of reserpine (1) usually leads to the anhydronium bases, 3,4-dehydroreserpine (2) and 3,4,5,6-tetradehydroreserpine (3), products of overall dehydrogenation. Indoles characteristically undergo autoxidation to produce primarily allylic indolenine hydroperoxides, which are susceptible to subsequent reactions by which other oxidation products are formed. The autoxidation of indole alkaloids has not been thoroughly examined. This work describes the characterization of the hitherto unreported major product of reserpine autoxidation, 6, formed in association with a minor proportion of the expected indolenine hydroperoxide, 5. Some evidence is advanced in support of a proposed mechanism of formation of these products.

Reserpine (1) reacts with a variety of reagents, undergoing oxidative dehydrogenation to produce the fluorescent anhydronium bases, 3,4-dehydroreserpine (3-dehydroreserpine) (2) and 3,4,5,6-tetradehydroreserpine ("lumireserpine") (3). Lead tetraacetate has been employed in their synthesis,[1] and vanadium pentoxide–phosphoric acid[2] and nitrous acid[3] reactions (which produce mainly 2) have been applied, with fluorescence detection, to the determination of reserpine in pharmaceutical formulations.

The nitrous acid reaction forms the basis of the official USP reserpine assay procedure[4] and has been investigated in some detail. Rescinnamine similarly produces the

(1) Wright, G. E.; Tang, T. Y. *J. Pharm. Sci.* **1972**, *61*, 299.
(2) Urbanyl, T.; Stober, H. *J. Pharm. Sci.* **1970**, *59*, 1824.
(3) Szalkowski, C. R.; Mader, W. J. *J. Am. Pharm. Assoc. (Sci. Ed.)* **1956**, *45*, 613. Banes, D.; Wolff, J.; Fallscheer, H. O.; Carol, J. *Ibid.* **45**, 710, **1956**.
(4) *The United States Pharmacopeia 21th rev*; U.S. Pharmacopeial Convention, Inc.: Rockville, MD, 1985; pp 935–940.

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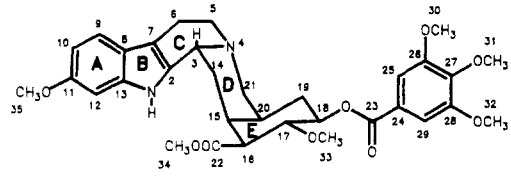
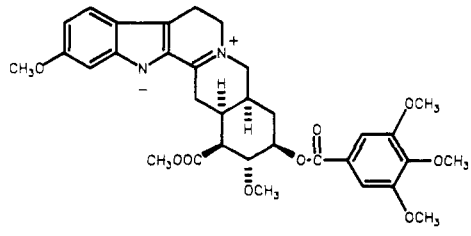
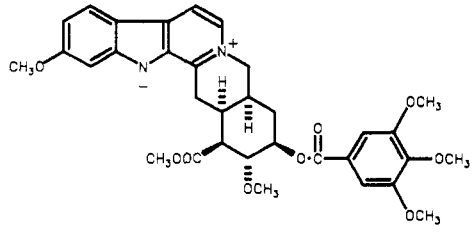
characteristic greenish-yellow reaction, but alkaloids such as alstonine, rauwolscine, sarpagine, raunescine, deserpidine, and yohimbine, which do not possess the 11-methoxy substituent, do not react.[5] A kinetic study[6] indicated that the reaction proceeds in two-step fashion, nitrous acid first reacting with protonated reserpine to form an intermediate, of as yet undetermined structure; the intermediate then decomposes under the influence of hydrogen ion to yield the 3,4-dehydro product. Interestingly, Weis-Fogh[7] has observed that 3-isoreserpine (4) "is also oxidized but the absorption in the green region is less, whatever the reason". Thin-layer chromatography of reserpine–nitrous acid reactions reveals that minor quantities of products other than 2 are formed, but only 3 has so far been identified;[8] this last study demonstrated, by HPLC, that 2 is the major degradation product in aged solid dosage forms of reserpine.



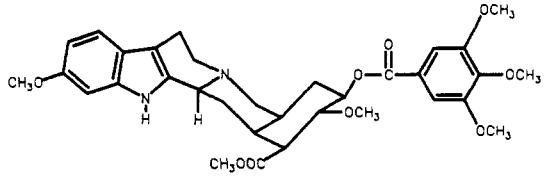
1 RESERPINE



2 3,4-DEHYDRORESERPINE



3 3,4,5,6-TETRADEHYDRORESERPINE



4 3-ISORESERPINE

There have been repeated reports of 3-isoreserpine (4) produced in solid dosage forms of reserpine,[9] but its identification is not reliable, being based solely on chromatographic retention times in single systems. Also, this pharmacologically inactive isomer of reserpine has been reportedly formed in aqueous solutions of reserpine exposed to daylight.[10] Ljungberg[11] has irradiated reserpine in chloroform and methanol solutions and identified (with the aid of paper chromatography) 2, 3, and 4 in the blue fluorescent darkened solutions: this author observed that both rescinnamine and deserpidine—the latter lacking the 11-methoxy substituent—were similarly photochemically transformed. A reserpine solution in THF, at room temperature under laboratory lighting for 5 days, produced 2 and 3, 2 the early major product and 3 eventually gaining ascendancy;[8] *no 3-isoreserpine* (4) was observed by an HPLC method which effected clean separation of reserpine and all three products.

Table I. EI Mass Spectral Data for Hydroperoxyreserpine (5) and Dioxyreserpine (6)

5		6	
m/z (%)		*m/z* (%)	
640 (<1)	[M^+]	640 (8.3)	[M^+]
624 (100)	[M^+ – 0]	624 (2.7)	[M^+ – 0]
607 (16.9)	[M^+ – OOH]	612 (1.3)	[M^+ – CO]
448 (66.7)		448 (11.1)	
434 (8.8)		436 (16.5)	
413 (12.1)		429 (53.6)	[M^+ – OTMB[a]]
395 (15.5)	[M^+ – OTMB – H_2O_2]	397 (8.0)	[M^+ – OTMB – O_2]
254 (12.7)		238 (8.2)	
238 (36.0)		212 (14.4)	[$HOTMB^+$]
212 (15.2)	[$HOTMB^+$]	195 (100)	[TMB^+]
195 (55.7)	[TMB^+]	177 (43.3)	[$C_9H_7NO_2^+$ + 0][b]

[a] TMB = Trimethoxybenzoyl group. [b] Corresponds to the loss of the oxindole ring system (rings A + B).

During the course of studies aimed at a more convenient synthesis of 2 and 3, employing the oxidizing agent (diacetoxyiodo)benzene (IBD),[12] a TLC spotting solution of reserpine in chloroform was left on the laboratory bench over the weekend. TLC of the solution on the following Monday morning revealed that reserpine had been substantially transformed to two products, one in predominant majority, different from 2, 3, and 4, by both TLC and HPLC analysis. Preparative TLC allowed isolation and quantitation of the products, isolated in 5:1 ratio, the total product estimated at roughly 40% conversion of reserpine. The reaction conditions were easily reproduced by simply placing a solution of reserpine in chloroform at room temperature in the presence of air and light. The reaction also proceeds, albeit at a slower rate, in other solvents such as methanol, ethyl acetate, and tetrahydrofuran. The reaction can be followed by HPLC using conditions to be described elsewhere.[13]

Elemental analyses showed these oxidation products to be isomeric oxygenated derivatives of reserpine, with molecular formula $C_{33}H_{40}N_2O_{11}$, corresponding to the addition of a molecule of oxygen. These results were confirmed by mass spectrometry (Table I), which showed molecular ions at *m/z* 640 for both products. No *N*-oxide formation, by oxygenation of the tertiary amine N-4, could be detected in the product solution; *N*-oxides have been shown to be the products of peracid treatment of tetrahydro-β-carboline alkaloids.[14]

The minor autoxidation product was obtained as a yellowish solid, mp 141–145 °C, which gradually turned brown on standing at room temperature in the presence of air. Its structure, the expected allylic indolenine hydroperoxide,[15] 7-hydroperoxy-7*H*-reserpine (5), was de-

(5) Haycock, R. P.; Mader, W. J. *J. Am. Pharm. Assoc. (Sci. Ed.)* **1957**, *46*, 744.
(6) Haycock, R. P.; Sheth, P. B.; Higuchi, T.; Mader, W. J.; Papariello, G. J. *J. Pharm. Sci.* **1966**, *55*, 826.
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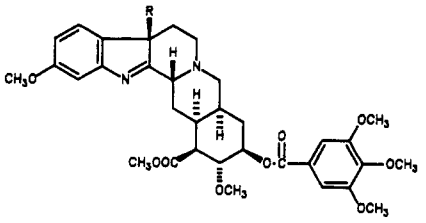
(11) Ljungberg, S. *J. Pharm. Belg.* **1959**, *14*, 115.
(12) Awang, D. V. C.; Vincent, A. *Can. J. Chem.* **1980**, 58, 1589.
(13) Girard, M.; Fillion, J.; Awang, D. V. C., manuscript in preparation.
(14) Ulshafer, P. R.; Taylor, W. I.; Nugent, R. H. *Compt. Rend.* **1957**, *244*, 2989.

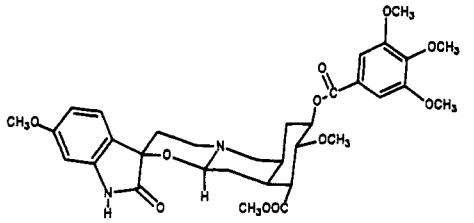
duced mainly using spectroscopic techniques. The fragmentation pattern observed in the mass spectrum (Table I) resembles that obtained for reserpine (1), showing loss of the trimethoxybenzoyl group (m/z 195 and 212) as one of the major fragmentation processes. Unlike reserpine, the parent ion corresponds to the loss of an oxygen atom, m/z 624, a process that has also been observed for another indolenine hydroperoxide.[16] The infrared (IR) spectrum also shows a close similarity to reserpine (1) in the region 800–1300 cm^{-1} and in the carbonyl absorption region where a broad carbonyl absorption band at 1725 cm^{-1} is observed. In addition, a strong hydroxyl absorption at 3450 cm^{-1} is present which can be attributed to the hydroperoxy group.

^1H and ^{13}C NMR analyses confirmed the identity of the minor product as 5; its ^{13}C NMR spectrum was very similar to that of 7-methoxy-7*H*-reserpine (7), prepared by the IBD–methanol reaction,[12] but for the additional methyl resonance due to the 7-methoxy substituent (Table II). The carbon chemical shift assignments for 7 were made using 2D proton spectra and ^{13}C–^1H correlation experiments in the same way as previously reported for reserpine.[17]



5 R = OOH 7-HYDROPEROXY-7H-RESERPINE

7 R = OCH_3 7-METHOXY-7H-RESERPINE



6 DIOXYRESERPINE

The major product of autoxidation, compound 6, which we commonly term "dioxyreserpine", crystallized from a mixture of methanol and ethyl acetate as tiny white needles, mp 178–180 °C. The presence of the intact trimethoxybenzoyl group was supported by fragments in the mass spectrum (Table I) at m/z 195, 212, and 429. The IR spectrum was devoid of strong absorption in the region 3200–3600 cm^{-1}, thus indicating the absence of hydroxyl group. Comparison of the ^{13}C data of reserpine[17] with those for dioxyreserpine (Table II) clearly shows that the oxidation occurs at the indole end of the molecule, the chemical shifts at the trimethoxybenzoate end being virtually identical for the two compounds. Two-dimensional proton spectra, combined with ^{13}C–^1H correlation, allowed the assignment of all protonated carbons. The quaternary carbons at the trimethoxybenzoate end of the molecule were assigned by comparison with reserpine.[17]

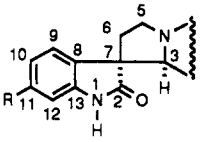
The proposed spiro oxindole–oxazine arrangement in 6 is reminiscent of part of the alkaloid isorhyncophylline,

Table II. ^{13}C Data for Reserpine and Related Compounds[a]

carbon	compounds 1[b]	5	6	7
1	–	–	–	–
2	130.49	184.62	178.11	182.37
3	53.79	54.48	87.04	54.50
4	–	–	–	–
5	51.28	50.04	47.90	49.84
6	16.81	36.80	31.78	36.91
7	107.97	81.26	74.43	86.84
8	122.21	133.00	122.72	128.74
9	118.53	122.68	125.26	122.92
10	108.97	110.87	107.39	111.45
11	156.18	161.73	161.33	161.21
12	95.26	107.43	97.22	107.29
13	136.41	154.62	141.16	155.49
14	24.31	22.35	29.29	22.13
15	34.00	31.58	36.16	31.27
16	51.82	52.29	51.79	51.93
17	78.03	77.74	77.93	77.85
18	77.90	78.40	78.08	78.01
19	29.77	29.82	30.27	29.56
20	32.33	34.74	34.05	34.46
21	49.02	49.19	57.29	48.90
22	172.87	172.96	171.65	172.49
23	165.49	165.92	165.47	165.29
24	125.38	125.90	125.44	125.35
25	106.83	107.43	106.64	106.74
26	153.00	153.47	153.00	152.85
27	142.32	143.02	143.30	142.18
28	153.00	153.47	153.00	152.85
29	106.83	107.43	106.64	106.74
30	56.26	56.54	56.31	56.15
31	60.78	61.03	60.90	60.77
32	56.26	56.54	56.31	56.15
33	60.91	61.03	60.90	60.70
34	51.82	52.05	51.79	51.72
35	55.76	55.63	55.58	55.46
OMe	–	–	–	51.83

[a] Spectra were obtained using $CDCl_3$ as solvent, and chemical shifts are expressed in δ ppm from TMS. [b] Data taken from ref 17.

Table III. Comparison of Observed and Predicted Carbon-13 Chemical Shifts of Oxindole Moiety



carbon	R = H[a]	R = OCH_3[b]	6
3	72.2	–	87.04
7	57.0	–	74.43
8	134.2	125.3	122.72
9	125.2	125.2	125.26
10	122.1	106.6	107.39
11	127.4	159.6	161.33
12	109.6	94.1	97.22
13	140.7	140.7	141.16

[a] Values taken from ref 18. [b] Predicted values using benzene additivity rules in ref 19.

except for presence of the C-11 methoxy substituent and the oxygen function between C-3 and C-7 in 6. Table III gives the reported[18] carbon-13 chemical shift values for isorhyncophylline, as well as values predicted for the aromatic ring with the addition of a C-11 methoxy substituent, using usual substituent effects.[19] Comparison

(15) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; p 282.
(16) Nakagawa, M.; Matsuki, K.; Haseganawa, K.; Hino, T. *J. Chem. Soc., Chem. Commun.* **1982**, 742.
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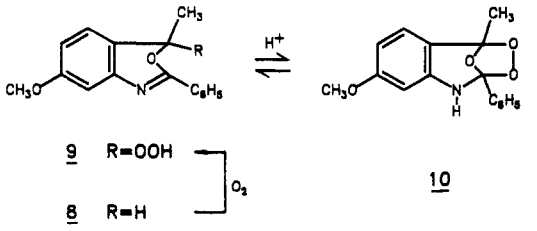
(19) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; p 197.

of the predicted values with those assigned in **6** shows good agreement (within 3 ppm). These carbons also showed all the expected correlations in the direct and long-range ^{13}C–^{1}H experiments, thus leaving only the assignments for C-2 and C-7. The signal at 178.11 ppm correlated only with the proton at δ 2.4 (C-6H), which is what would be expected for C-2. The remaining carbon resonance (δ 74.43) correlated with protons at δ 2.4 (C-6H), 2.7 (C-5H), 7.2 (C-9H), and 8.4 (NH), confirming its assignment as C-7. It is interesting to compare the chemical shifts of C-3 and C-7 for isorhyncophylline and dioxyreserpine (Table III). Both carbons are shifted to lower field in **6** by 15 and 17 ppm, respectively. Although a more substantial downfield shift might have been predicted on the basis of additivity rules, the chemical shift for C-3 in **6** is comparable to those reported for other compounds containing an oxazine carbon, such as geissospermine[20] (80.6 ppm) and an alkaloid extracted from *Voacanga africana*[21] (82.0 ppm). It would not be unreasonable to expect a similar change in chemical shift for C-7 as that for C-3, consistent with the observed value.

The chemical shifts of C-5, C-15, and C-21 indicate that the C/D ring junction, which is cis in reserpine, is trans in the dioxy product **6**. Coupling constants provide strong support for the trans C/D ring junction. Thus, in **6** $J_{3,14eq}$ = 3.3 Hz and $J_{3,14ax}$ = 9.7 Hz (compared with 3.0 and 5.0 Hz, respectively, in reserpine). Simultaneously, $J_{14ax,15}$ is 13.7 Hz in **6**, which immediately shows that C-3H and C-15H must be on the same side of the ring and the C/D junction trans. Further evidence for the trans ring junction comes from an NOE difference experiment for the proton on C-3, in which essentially equal size responses were found for the proton on C-15 and a proton on C-5. This NOE difference experiment also served to determine the configuration at the spiro center C-7, since a positive response was found for the amide proton.

Dioxyreserpine (**6**) is an unusual product, not previously recognized and apparently particular to the 7-methoxy-β-carboline structure, since deserpidine, the desmethoxy analogue of reserpine, seems completely passive under similar exposure to air. An interesting parallel, which further impresses the importance of that critically situated methoxy substituent, is found in Witkop's investigation of autoxidation and ozonolysis of simple indoles.[22] In his attempts to convert an oxazine (**8**) to an oxazine hydroperoxide (**9**), isomeric with Staudinger's isoozonide (**10**), Witkop found that autoxidation would not proceed readily without the appropriately situated methoxy group.



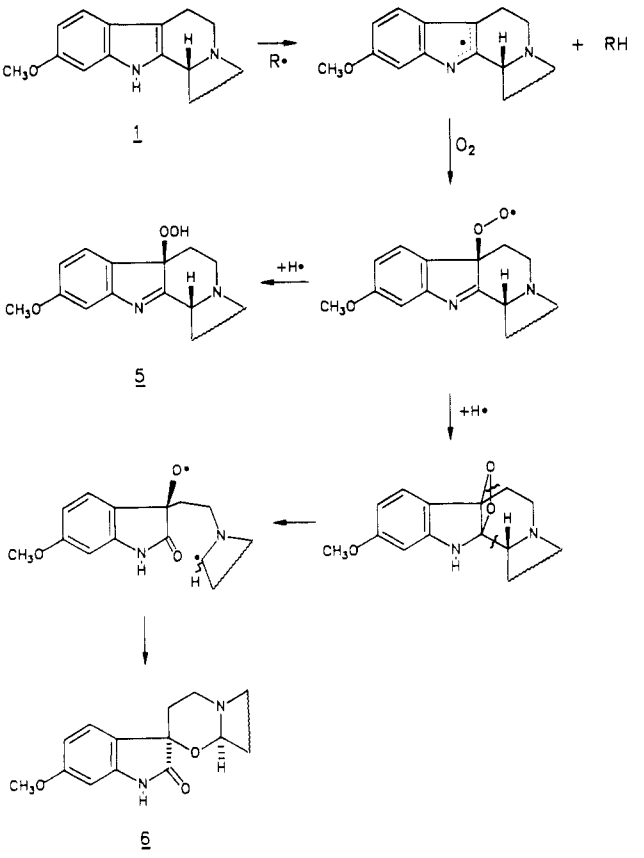
9 R=OOH

8 R=H

10

The formation of **6**, a rare spiro oxindole–oxazine,[23] is reminiscent of the synthetically useful formation of spirooxindoles from chloroindolenines.[15,24] A plausible mechanism would seem to be addition of oxygen to the mesomeric radical formed in an initiating step by abstraction of the hydrogen attached to indole nitrogen, as illustrated in Scheme I. The formation of a dioxetan anion (negatively charged indole nitrogen) of similar structure is supported by examination of the decomposition of hydroperoxyindolenines.[25] Saturation of carbon 2 in tetrahydro-β-carboline indole alkaloids has been proposed as the driving force behind rearrangement of chloroindolenines to the imino ether precursors of spirooxindoles,[26] and rate/differences rationalized on the basis of stereochemical considerations.[24] The particular rearrangement observed in the present case is undoubtedly facilitated by the weak O–O bond, as earlier observed by McCapra and Long.[25] Bond fission between C-2 and C-3, coincident with O–O cleavage, would lead to amide formation. Inversion of configuration of the C-3 hydrogen could simply be a reflection of the natural choice of the more stable configuration with respect to the N-4 lone pair. The minor hydroperoxide product **5** would be formed by less competitive hydrogen abstraction from solvent by the initially formed oxygen-radical adduct. (Clearly compound **5** is not an intermediate in the formation of its isomer **6**, since no conversion of **5** to **6** has been evident in solutions of **5** exposed to the conditions under which **6** is formed from reserpine.) The electron-donor character of the methoxy substituent would be expected to enhance the rate of oxygen addition to the indole–indolenine π-system. The importance of the cis arrangement of C-3H and N-4 lone pair is reflected in failure of 3-isoreserpine (the trans isomer of reserpine) to produce a corresponding spiro-

Scheme I. A Plausible Mechanism of Formation of Reserpine Autoxidation Products



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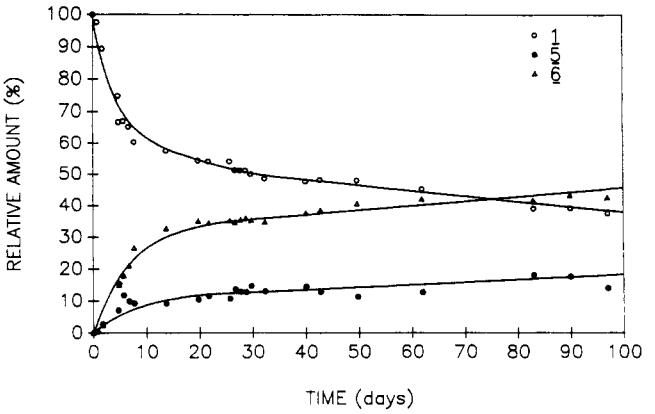

Figure 1. Plot of degradation of reserpine (1) and formation of hydroperoxyreserpine (5) and dioxyreserpine (6) from HPLC studies.

oxindole on protracted exposure to light and air.

An alternate mechanism, involving abstraction of C-3 hydrogen, was discredited by experiments with reserpine deuterated at C-3. The rearranged product, **6**, exhibited no protium incorporation as would be expected if abstraction of C-3 deuterium were a significant mechanistic process.

The rate of formation of autoxidation products **5** and **6** was followed by HPLC and the results are presented in Figure 1. In both cases, very rapid formation occurs in the initial days of reaction. Thus, within 5 days, 35% of reserpine has reacted, rising to 40% in the next 5 days. The rate of formation of dioxyreserpine (**6**) itself is initially more rapid than that of the hydroperoxy compound **5**, leading to a ratio of 3:1 in favor of **6** after 15 days. This ratio slowly decreases to 2.25:1 after 100 days. The relative instability of the hydroperoxy compound **5** may explain the higher ratio of products (5:1) observed upon isolation of the individual compounds.

Experimental Section

Instrumentation. All NMR spectra were recorded at 300 K on a Bruker AM360 or AM400 spectrometer equipped with an Aspect 3000 computer and process controller, using DISNMR version 870101. Standard microprograms from the Bruker Software Library were employed. The ^1H–^1H COSY experiments used N-type phase cycling with a 45° mixing pulse. The long-range experiments used an 80-ms delay. The ^1H–^{13}C COSY spectra were obtained using composite-phase decoupling with polarization transfer from ^1H to ^{13}C. The raw data were zero-filled in F1 prior to FT, the sine-bell window function being used in both F1 and F2. A proton relaxation delay of 5 s was used. For long-range correlations, the delays were chosen to emphasize couplings of ca. 4, 7.5, and 12 Hz. The ^1H–^1H NOE difference experiments were carried out using the microprogram from the standard Bruker library. Data were acquired with the decoupler gated off (relaxation time = 2.0 s) after an irradiation time of 2.0 s. After subtraction of the off-resonance control FID from those of the other decoupling frequencies, the resulting FID's were processed with a line broadening of 2 Hz. Infrared spectra were obtained on a Nicolet Fourier transform spectrometer as KBr pellets. Mass spectra were measured on a Finnigan-Mat spectrometer using a direct probe exposure (DEP). All analytical HPLC separations were performed on a Spectra-Physics 8100 chromatograph, coupled to a Kratos UV–vis detector operating at 230 nm. Preparative HPLC separations were made using a Waters HPLC system equipped with Model M-6000 pump and Model 440 UV detector operating at 254 nm. Optical rotations were measured on a Perkin-Elmer polarimeter, using the sodium D line. Melting points were obtained on a Fisher-Johns hot plate and are uncorrected. Thin-layer chromatography (TLC) experiments were made on precoated silica gel plates (Merck) with fluorescent background and using ethyl acetate for elution.

Materials. Reserpine and deserpidine were purchased from Aldrich. 7-Methoxy-7*H*-reserpine was obtained as described earlier.[12] All solvents used were distilled-in-glass or HPLC grades. Analytical HPLC separations were performed on reverse-phase RP18 (Brownlee) columns (4.5 mm × 250 mm, 10 μ), using solvent system A, 0.005 M potassium phosphate monobasic (containing 0.06% (v/v) of triethylamine and adjusted to pH 3.50 with phosphoric acid)/acetonitrile, 39:61, at a flow rate of 1 mL/min,[13] or on PLC-18 Supelcosil (Supelco) columns (4.5 mm × 250 mm, 18 μ), using solvent system B, methanol/water, 80:20, at a flow rate of 1 mL/min. Preparative separations were done on PLC-18 Supelcosil (Supelco) columns (21.2 mm × 250 mm, 18 μ) using solvent system B followed by a final HPLC purification with solvent system C, methanol/water/chloroform, 62:33:5.

Autoxidation of Reserpine. In a typical experiment, reserpine (1 g) was placed in chloroform (100 mL) and allowed to stand at room temperature, in the presence of air, in a lighted area, for 15 days (ca. 50% conversion). The initial colorless solution gradually turned yellow. The resulting solution was transferred to a round-bottom flask and evaporated to dryness under reduced pressure. The solid residue was dissolved in ethyl acetate and passed through a small column packed with Florisil in order to remove minor polar constituents. Separation of the resulting solution was accomplished by preparative HPLC using the method described above to obtain 60 mg of **5** (5.8%) and 295 mg of **6** (28.1%) as well as unreacted reserpine.

Dioxyreserpine (6), the major autoxidation product (lower R_f product by TLC), was recrystallized from methanol/ethyl acetate to give tiny, white needlelike crystals: mp 178–180 °C; $[\alpha]_D$ −78.8° (*c* 0.10, $CHCl_3$); UV λ_{max} (nm) in EtOH 214, 266 (log ε 4.97, 4.35); IR ν_{max} (cm^{-1}) in KBr 1725 (br); MS, see Table I; ^1H NMR δ (ppm) in $CDCl_3$ 3.50 (3 H, s, C-33H_3), 3.67 (3 H, s, C-34H_3), 3.78 (3 H, s, C-35H_3), 3.91 (3 H, s, C-31H_3), 3.93 (6 H, s, C-30H_3 and C-32H_3), 4.59 (1 H, dd, C-3H), 5.01 (1 H, m, C-18H), 6.38 (1 H, d, C-12H), 6.55 (1 H, dd, C-10H), 7.25 (1 H, d, C-9H), 7.34 (2 H, s, C-25H and C-29H), 7.57 (1 H, bs, NH); ^{13}C NMR δ (ppm) in $CDCl_3$, see Table II. Anal. Found: C, 61.69; H, 6.34; N, 4.26; O, 27.71. Calcd for $C_{33}H_{40}N_2O_{11}$: C, 61.87; H, 6.25; N, 4.37; O 27.51.

Hydroperoxyreserpine (5), the minor autoxidation product (higher R_f product by TLC), was obtained as a yellowish solid: mp 141–145 °C; UV λ_{max} (nm) in EtOH 212, 265 (log ε 4.81, 4.15); IR ν_{max} (cm^{-1}) in KBr 3450, 1725 (br); MS, see Table I; ^1H NMR δ (ppm) in $CDCl_3$ 3.50 (3 H, s, C-33H_3), 3.82 (6 H, s, C-34H_3 and C-35H_3), 3.92 (9 H, s, C-30H_3, C-31H_3, and C-32H_3); ^{13}C NMR δ (ppm) in $CDCl_3$, see Table II. Anal. Found: C, 60.44; H, 6.32; N, 4.28; O, 28.96. Calcd for $C_{33}H_{40}N_2O_{11}$: C, 61.87; H, 6.25; N, 4.37; O, 27.51. (The discrepancy between the calculated and observed values is likely due to the apparent instability of the product, evident in its rapid discoloration.)

[3-^{2}H]Reserpine. The preparation of reserpine deuterated at C-3 was accomplished by conversion of reserpine to its oxidation product, 3,4-dehydroreserpine (**2**),[27] followed by zinc reduction[28] of the oxidized product in a deuterated medium. In a typical procedure, trifluoroacetic acid (0.1 mL, 1.2 mmol) was added dropwise to a solution of reserpine (0.061 g, 0.1 mmol) in acetic acid (10 mL), with O_2 bubbling continuously for 72 h. The resulting yellow solution was evaporated under reduced pressure, and the bright yellow residue was triturated with a small amount of methanol. The yellow solid thus obtained was treated with hot methanol, and the white precipitate formed after cooling of the solution was removed as it is composed almost entirely of unoxidized reserpine. Repeated treatment with hot methanol afforded a reserpine-free solution that was evaporated to dryness under reduced pressure to give a bright yellow viscous liquid. The residue was then dissolved in 50% (v/v) CD_3COOD/D_2O (3 mL), and Zn dust was added. The solution was stirred at room temperature for 2 h, after which time the yellow coloration had disappeared. The zinc salts were removed by filtration, and the remaining solution was neutralized using 5 N NaOH solution. Extraction with chloroform (3 × 5 mL), followed by washing of the organic layer with water and drying over sodium sulfate, afforded a viscous colorless liquid, which showed presence of a

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single compound by TLC. Analysis by MS and ^1H NMR revealed that the product was a mixture of monodeuterated and dideuterated reserpine, where complete deuteration at C-3 had occurred since the expected C-3H signal at δ 4.50 ppm had disappeared. The site of the second deuterium could not be identified with certainty, but presumably partial deuterium exchange occurred in the α-position of the carbomethoxy group at C-16.

Autoxidation of [3-^{2}H]Reserpine. Deuterated reserpine was placed in chloroform and allowed to autoxidize following the procedure established above. After completion, the residue was separated by HPLC to afford dioxyreserpine which had retained the deuterium at the same positions as in the starting reserpine. This was indicated by data from MS where the compound features a molecular ion at m/z 641, indicating retention of a deuterium atom, and from ^1H NMR where the absence of a signal at 4.60 ppm, corresponding to C-3H in **6**, confirmed the position of attachment of the deuterium atom.

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Notes

Exploring the Chemistry of the 2-Arylhexafluoro-2-propanol Group: Synthesis and Reactions of a New Highly Fluorinated Monomer Intermediate and Its Derivatives

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Since the early 1960s, various reports of monomers and polymers containing the 2,2-diaryl-1,1,1,3,3,3-hexafluoropropyl group have appeared.[1] The impetus for this activty has been the often improved solubility, thermal stability, chemical inertness, mechanical properties, and electrical properties exhibited by these polymers. In an effort to produce colorless, transparent, and heat-stable coatings for aerospace applications, we have synthesized diol monomer intermediate **3** (Scheme I), which contains three 1,1,1,3,3,3-hexafluoroisopropyl groups. We now report the synthesis of diol **3**, the chemistry of it and some of its derivatives, and the successful synthesis of two high molecular weight polymers which have the diol **3** incorporated into the backbone.

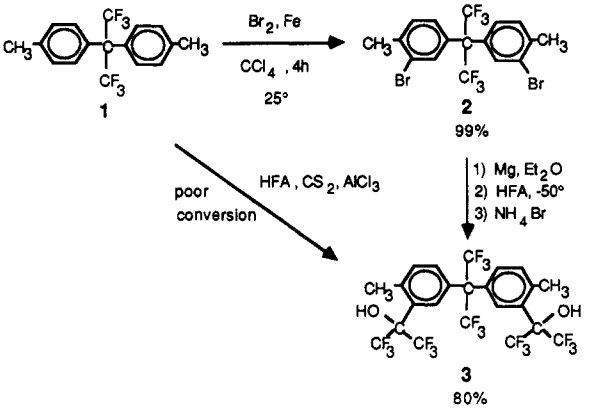
Diol **3** was prepared in two steps from 2,2-bis(4'-tolyl)hexafluoropropane (**1**) (courtesy of Hoechst Celanese Co.) by treatment of the Grignard reagent derived from the intermediate dibromide **2** with hexafluoroacetone (HFA) as shown in Scheme I.

The initially attempted direct hydroxyalkylation of **1** under Friedel–Crafts conditions gave only low conversions to the diol.

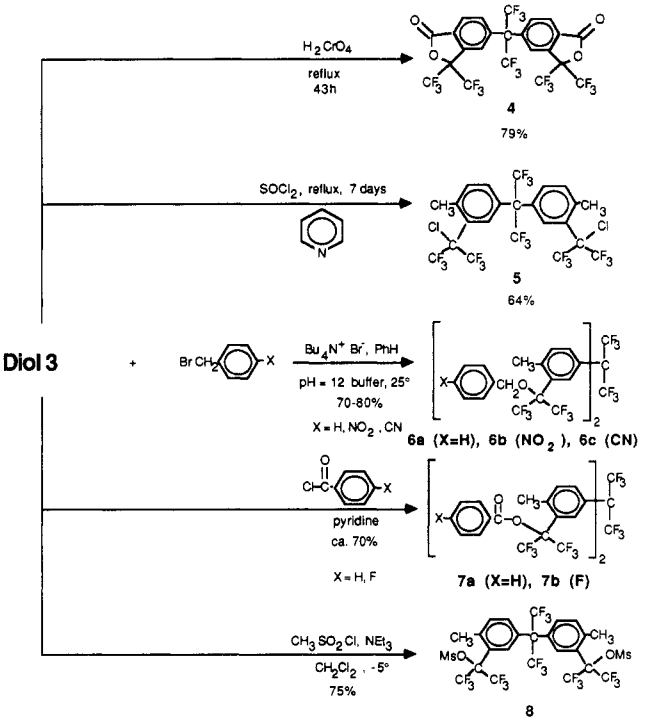
Diol **3** was successfully reacted under a variety of conditions to afford several derivatives as shown in Scheme II.

These transformations included oxidation to form bisphthalide **4**, chlorination,[2] Williamson ether syntheses with benzyl bromides under phase transfer conditions,[3] esterification, and mesylation. In contrast, the diol **3** failed to react under Friedel–Crafts conditions with anisole [(a)-

Scheme I



Scheme II



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