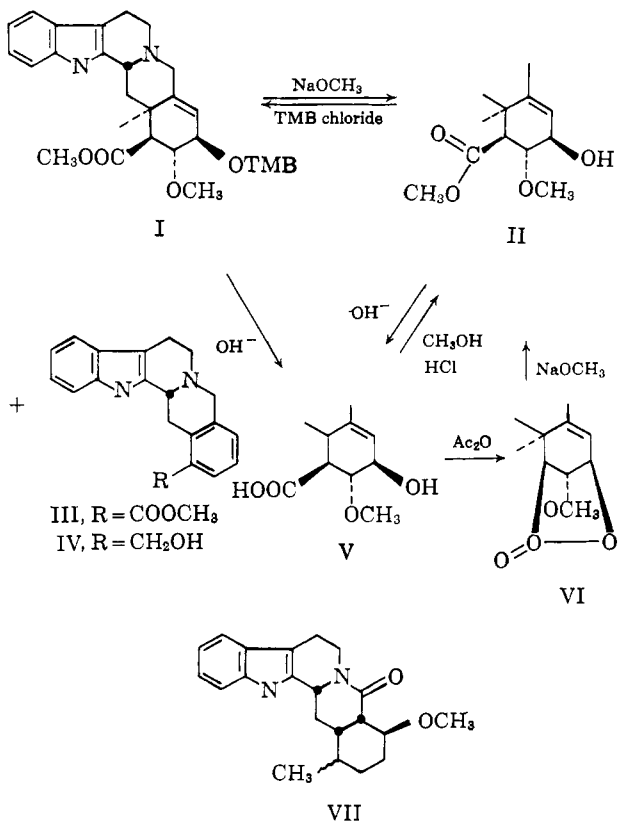
Deserpideine, a New Yohimbinoid Type Alkaloid

Sir:

From the weakly basic fraction of *Rauwolfia nitida Jacq.*, we have isolated the new indole alkaloid deserpideine (I), $C_{32}H_{36}O_8N_2$, m.p. 149–152°, $[\alpha]^{25}D$ −133° (pyridine), whose infrared and ultraviolet spectra are very close to those of deserpidine.

Sodium methoxide treatment of I gave the expected methyl deserpideate (II), $C_{22}H_{26}O_4N_2 \cdot H_2O$, m.p. 159–162°, $[\alpha]^{25}D$ +8° (pyridine), methyl trimethoxybenzoate, and a rather unstable dextrorotatory compound, $C_{21}H_{20}O_2N_2 \cdot 0.5C_2H_5OH$, m.p. 174–176°, $[\alpha]^{25}D$ +288° (pyridine), molecular ion peak at *m/e* 332, λ_{max}^{EtOH} 223 mμ (ε 49,700) and 282 (10,500), infrared peak at 5.83 μ (conjugated ester), which has been characterized as 11-demethoxytetrahydroalstoniline (III). $LiAlH_4$ reduction of III gave the alcohol IV, hydrobromide salt m.p. 300° dec. Racemic IV was then synthesized according to Elderfield[1] from isoquinoline-5-carboxylic acid, and the two hydrobromide salts were found to have identical infrared spectra (KBr disks).

Hydrolysis of either I or II gave deserpideic acid (V), $C_{21}H_{24}O_4N_2$, m.p. 224–226°, $[\alpha]^{25}D$ −29° (50% CH_3OH–H_2O), which could be converted to deserpideic acid lactone (VI), $C_{21}H_{22}O_3N_2$, m.p. 159–161°, $[\alpha]^{25}D$ −58° (50% CH_3OH–H_2O), on treatment with acetic anhydride. Methyl deserpideate could also be prepared by allowing the lactone VI to stand at 0° in sodium methoxide in methanol (80% yield), while I could be reconstituted by treatment of II with trimethoxybenzoyl chloride.



The presence of a double bond at C-19(20) was first indicated by a very fast rate of methiodide formation for I ($k = 3 \times 10^{-2}$ sec.$^{-1}$) which indicated that, unlike deserpidine, N_b in deserpideine must be unhindered.[2,3] Furthermore, the n.m.r. spectrum of deserpideine in deuteriochloroform showed a vinylic proton absorption at 5.6 p.p.m., superimposed on the absorption of the C-18 hydrogen. The n.m.r. spectrum of methyl deserpideate showed an isolated vinylic absorption at 5.6 p.p.m., with the C-18 hydrogen further upfield. Finally, the mass spectra of methyl deserpideate and deserpideic acid lactone showed molecular ion peaks at *m/e* 382 and 350, respectively, results which again indicate the presence of an unsaturation in the two derivatives.

To settle conclusively both the position of the double bond and the stereochemistry of deserpideine, the alkaloid was reduced with Adams catalyst in ethanol solution at room temperature and atmospheric pressure. The product turned out to be a complex mixture which gave at least ten spots on a silica gel chromatogram, and was divided into an acidic, a basic, and a neutral fraction. The acidic material, which was obtained in 70% yield, was fully characterized as trimethoxybenzoic acid by means of its infrared spectrum, its melting point, and its mixture melting point. Trituration of the basic material in ethyl acetate gave a crystalline compound, recrystallized from ethyl acetate, m.p. 225–226°, $[\alpha]^{25}D$ −123 ± 7° ($CHCl_3$). The R_f values and n.m.r. and infrared spectra of this compound were identical with those of authentic deserpidine, and a mixture melting point showed no depression. The sample of authentic deserpidine exhibited $[\alpha]^{25}D$ −120° ± 5° ($CHCl_3$).

From the neutral fraction, the crystalline lactam VII, $C_{21}H_{26}N_2O_2$, was obtained, m.p. 245.5–247.5° dec., $[\alpha]^{25}D$ +142 ± 3° ($CHCl_3$), infrared peak at 6.13 μ (lactam), C–CH_3 doublet at 1.03 p.p.m. and O–CH_3 singlet at 3.25 p.p.m. Catalytic reduction of I, therefore, can result in hydrogenation of the 19(20) double bond and hydrogenolysis of the 21(4) C–N bond and the C-18–oxygen bond. Deserpideine must thus have the same stereochemistry and absolute configuration as deserpidine, with the ubiquitous α-H at C-15.

Similarly, catalytic reduction of methyl deserpideate led to the isolation, from the basic cut, after repeated preparative thin layer chromatograms on silica gel, of amorphous methyl deserpidate, identical with authentic methyl deserpidate (infrared spectra in chloroform and in acetonitrile solutions, R_f values, and n.m.r. spectra). Acceptable elemental analyses were obtained for all the compounds in question.

Deserpideine is thus the first member of the 19-dehydroyohimbinoid alkaloids to be characterized, and interestingly enough the alkaloid still retains about 60% of both the sedative and hypotensive activity of reserpine. The possible relationship between deserpideine and raujemidine, which also has a fast rate of methylation,[3] is presently being investigated.

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(1) R. C. Elderfield and B. A. Fischer, *J. Org. Chem.*, **23**, 949 (1958).

(2) M. Shamma and J. M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963).

(3) M. Shamma and E. F. Walker, Jr., *Chem. Ind.* (London), 1866 (1962).

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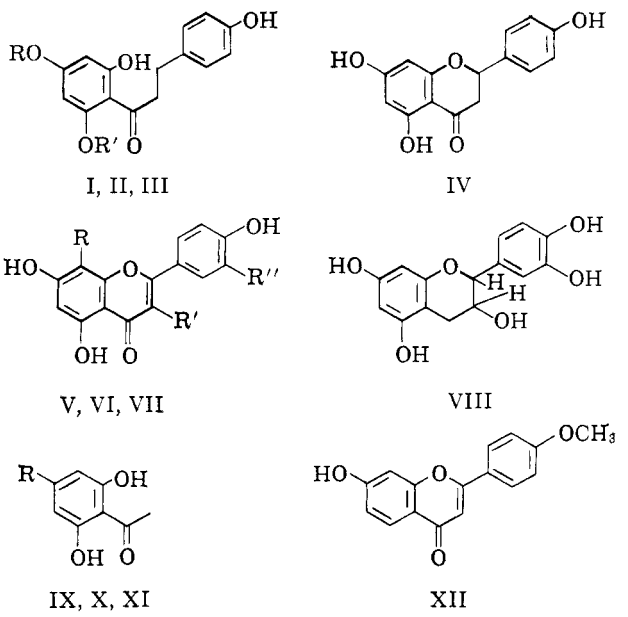
Nuclear Hydrogen–Deuterium Exchange in Resorcinols and Related Compounds in Weakly Alkaline Solution

Sir:

Under forcing alkaline conditions all hydrogen atoms of the phenoxide anion can be replaced by deuterium,[1,2] while under somewhat less stringent conditions only the *ortho* and *para* hydrogens exchange.[3] In either case the reaction is slow. We have found that the presence of a second hydroxy group, when oriented *meta*, greatly enhances the rate of exchange; mild reaction conditions then suffice for complete (*i.e.*, equilibrium) exchange of the *ortho* and *para* hydrogens.

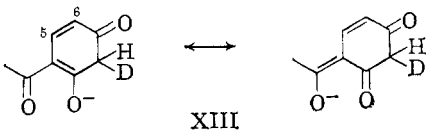
The exchange was monitored by n.m.r. spectroscopy in deuterium oxide solutions of approximate pH 9. In some cases, after the exchange was complete, the sample was diluted with water and the reappearance of the peak(s) observed.[4] The spectra of phenol, catechol, and hydroquinone in alkaline deuterium oxide did not change during several hours and were the same as their spectra in water. In contrast, the exchange of protons 2, 4, and 6 of resorcinol reached equilibrium in 1 hr. at pH *ca.* 8 and in 10 min. at pH *ca.* 11. The hydrogens in phloroglucinol also exchanged rapidly. Other compounds, listed below, showed the following behavior: (1) the combined activating effects of two or more *meta*-oriented OH groups sufficed for ready exchange of protons *ortho* and *para* to them (I–XI); (2) protons of aromatic rings containing only one OH group (I–VI) or two adjacent OH groups (VII and VIII) did not exchange; (3) the OR of the pyrone ring *meta* to an OH group did not serve in lieu of the second OH (none of the protons in XII exchanged); (4) the various protons α to a ketone (I–IV, IX–XI) exchanged, but much more slowly than the aromatic ones (see below, however).

The exchangeable nuclear protons in compounds III–V, VII, and VIII are nonequivalent and the proton absorbing at higher field exchanged more rapidly.[5] In 4-acetylresorcinol the exchangeable protons can be distinguished from each other since the signal due to H-6 exhibits the usual *ortho* coupling of ~9 c.p.s. The proton flanked by the two OH groups (H-2) exchanged readily, but H-6 was replaced rapidly only on heating; the methyl ketone protons exchanged more rapidly



I, phloretin, R = R′ = H. II, naringin dihydrochalcone, R = 2-*O*-α-L-rhamnosyl-β-D-glucosyl; R′ = H. III, phloridzin, R = H; R′ = β-D-glucosyl. IV, naringenin. V, apigenin, R = R′ = R″ = H. VI, vitexin, R = *C*-β-D-glucosyl; R′ = R″ = H. VII, quercitrin, R = H; R′ = α-L-rhamnosyloxy; R″ = OH. VIII, *d*-catechin. IX, R = H. X, R = 2-*O*-α-L-rhamnosyl-β-D-glucosyloxy. XI, R = OH. XII, pratol.

than H-6, but much more slowly than H-2. The slowness of H-6 exchange becomes understandable if delocalization of the negative charge in the intermediate XIII is greatly enhanced by the acetyl group. Formation of an sp^3 center at C-6 precludes such interactions.



XIII

In 4-carboxyresorcinol H-2 also exchanged faster than H-6, and in both compounds the peak due to H-2 was slightly upfield. However, in 4-chlororesorcinol, H-6 exchanged faster and its absorption was slightly upfield; and in 5-carboxyresorcinol H-4 and H-6 exchanged faster than H-2, although H-2 absorbed at higher field. Thus, no general direct relationship exists between the effect of substituents on the chemical shift of a particular proton and their effect on the rate of exchange.

Several naphthalenediols were examined to ascertain whether all protons that can, in principle, be activated by both OH groups do exchange. As expected, no exchange occurred in 1,5-naphthalenediol. While H-1 and H-8 in 2,7-naphthalenediol were rapidly replaced by deuterium, the other protons were unaffected even on heating.[6] In 1,6-naphthalenediol H-2, H-4, and H-5 exchanged.[7] A path for exchange is *via* ketone–enolate

(1) A. I. Shatenshtein and A. V. Vedeneev, *Zh. Obshch. Khim.*, **28**, 2644 (1958); *Chem. Abstr.*, **53**, 5836 (1959).

(2) G. E. Hall, E. M. Libby, and E. L. James, *J. Org. Chem.*, **28**, 311 (1963).

(3) A. P. Best and C. L. Wilson, *J. Chem. Soc.*, 28 (1938); C. K. Ingold, C. G. Raisin, and C. L. Wilson, *ibid.*, 1637 (1936); *cf.*, however, P. A. Small and J. H. Wolfenden, *ibid.*, 1811 (1936).

(4) For comparison, spectra of most compounds were determined in water at the same pH. The spectra varied according to the amount of anion present: signals due to protons *ortho* to an OH group were always shifted upfield as more of the anion was formed, while signals due to the *meta* protons were either unaffected or shifted downfield.

(5) In naringenin (IV) the chemical shifts of these protons coincided so that a difference in the exchange could not be ascertained. Catechin (VIII) decomposed at higher pH, but could be recovered from solution at pH 8 in which its exchange was very fast.

(6) Exchange occurred also in 2-naphthol. By analogy with 2,7-naphthalenediol, it was assumed that this takes place at H-1. R. F. W. Cieciuch and P. C. Morrison have analyzed the splitting pattern of the 2-naphtholate ion and determined that the exchange does occur at H-1. We thank Dr. Cieciuch for permission to cite these results in advance of publication.

(7) The positions of exchange were deduced as follows: after exchange the spectrum showed a typical AB system (J ~ 9 c.p.s.) as well as a singlet. Since the low-field part of the AB system was also apparent prior to exchange (the high-field part overlapped with the complex multiplet due to the other protons except H-2 which appeared as a quartet at higher field) and since H-8 is the only proton in the nondeuterated compound that would ordinarily be expected to couple with only one proton, *i.e.*, H-7, the AB system in the spectrum of the deuterated compound must be due to H-7 and H-8. The singlet is assigned to the *meta* hydrogen, H-3.