

Here, ring expansion predominates over the alternative reactions: possible Arbuzov-type displacement by oxygen on alkyl carbon to give the phosphonate<sup>5</sup> or reverse aldol-type ring opening, which then would lead to identical products from either I or VIII as with amines and alkoxide ions.<sup>4</sup> Likely, neutralization of the positive charge developed on phosphorus and release of four-membered ring strain are the reaction driving forces.

Further work, *e.g.*, determination of migrational selectivity in reaction of mixed phosphites, is in progress.

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### Acid- and Base-Catalyzed Hydrogen Exchange in Methyl-Substituted Indoles<sup>1</sup>

Sir:

The exchange of isotopic hydrogen on the indole nucleus was first reported by Koizumi<sup>2</sup> for the heterogeneous system of molten indole and aqueous solutions containing some deuterium. These early studies established the position and number of hydrogen atoms ex-

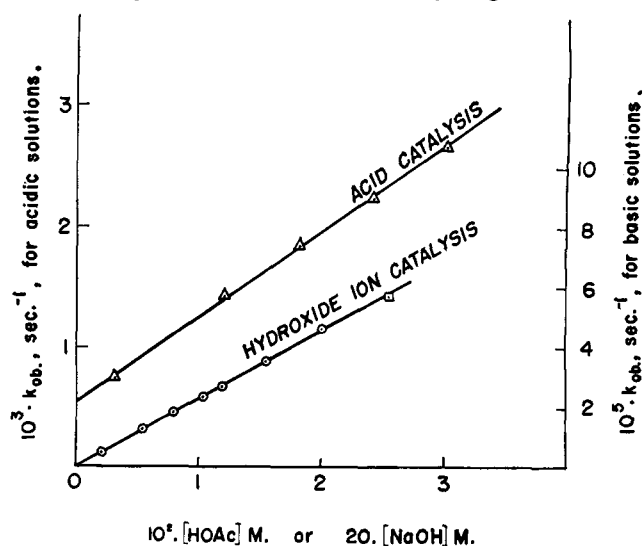


Figure 1.

changed, but not the mechanism of the process. More recently Hinman and Whipple<sup>3</sup> studied the position of protonation to form the conjugate acid in several substituted indoles and reported the rates of homogeneous exchange with deuterated solvents for various positions of the heterocyclic ring. Their nuclear magnetic resonance technique required relatively high acid con-

centrations, which complicates the elucidation of the reaction mechanism.

The detritiation of 2-methylindole-3-*t* in a homogeneous aqueous solution proceeds with a convenient rate at 25° in the pH range from 4 to 6. The reaction is catalyzed by the hydronium ion and general acids. This is illustrated by the data of the accompanying figure, where the observed first-order rate coefficient  $k_{ob}$  ( $v = k_{ob}[2\text{-methylindole-3-}t]$ ) is plotted against the concentration of acetic acid for reaction in acetic acid-sodium acetate buffers at a pH of 5.01 and at an ionic strength of 0.1. The rate law of the exchange reaction is

$$k_{ob} = 42[\text{H}_3\text{O}^+] + 0.071[\text{HOAc}]$$

Similar studies for other carboxylic acids lead to a value of 0.58 for the Brønsted  $\alpha$  factor. A more extensive Brønsted plot, embracing a series of acids extending to the hydronium ion, is not linear, indicating that the acid type, as well as its strength, is important in determining the degree of catalysis.

The acid-catalyzed detritiation of 1,2-dimethylindole-3-*t* in acetic acid-sodium acetate buffer solutions follows a similar rate law to that observed for 2-methylindole-3-*t*

$$k_{ob} = 72.4[\text{H}_3\text{O}^+] + 0.176[\text{HOAc}]$$

The greater reactivity of the disubstituted indole, compared to 2-methylindole-3-*t*, is in accord with the reported basicity<sup>4,5</sup> of the 3-position for the two compounds.

The observed general acid catalysis strongly suggests that the exchange process in acidic solutions occurs *via* the A-SE2 mechanism recently proposed for the isotopic hydrogen exchange of azulene<sup>6</sup> and 1,3,5-trimethoxybenzene.<sup>7</sup>

A point of considerable interest is that the detritiation of 2-methylindole-3-*t* is also catalyzed by hydroxide ion. A plot of the observed first-order rate coefficient ( $k_{ob}$ ) against the hydroxide ion concentration, at a constant ionic strength of 0.1, is linear, as shown in the figure. The value of  $k_{OH^-}$  ( $v = k_{OH^-}[2\text{-methylindole-3-}t][\text{OH}^-]$ ) at 25° is  $4.5 \times 10^{-4}$  mole<sup>-1</sup> l. sec.<sup>-1</sup>. In contrast to the results for acid catalysis, the rate of detritiation of 1,2-dimethylindole-3-*t* in alkaline solutions is much slower than that observed for 2-methylindole-3-*t*. Thus for a hydroxide ion concentration of 0.126 M the rate of tritium exchange for 1,2-dimethylindole-3-*t* is only  $1.41 \times 10^{-7}$  sec.<sup>-1</sup>, which approximates closely to the rate expected for the "spontaneous" catalysis by the aqueous medium itself. We therefore conclude that, within the limits of experimental error, there is no catalysis by hydroxide ion.

It is unlikely that the base-catalyzed exchange stems from a direct attack of hydroxide ion on the isotopic hydrogen attached to the 3-carbon, since for both the 1,2-dimethyl and 2-methyl derivatives this site is known to be basic, rather than acidic. The striking reversal of relative reactivity of the two compounds, on going from acidic to basic solutions, suggests that the strong base catalysis observed for 2-methylindole-3-*t* requires the presence of a labile amino-hydrogen atom. An attack of hydroxide ion on the indolenine tautomer is ruled out because the tautomerism itself would lead to rapid exchange of the tritium label. The most probable explanation, then, is an attack of water, acting as a general acid, on the anion of 2-methylindole-3-*t* formed by proton loss from the nitrogen. 1,2-Dimethylindole-3-*t* is unable to form a comparable anion, and the ex-

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(1) Work supported by a grant from the Atomic Energy Commission.

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change rate in basic solutions, proceeding solely *via* the attack of water on the neutral molecule, therefore is markedly slower. Further work on these and related compounds is in progress.

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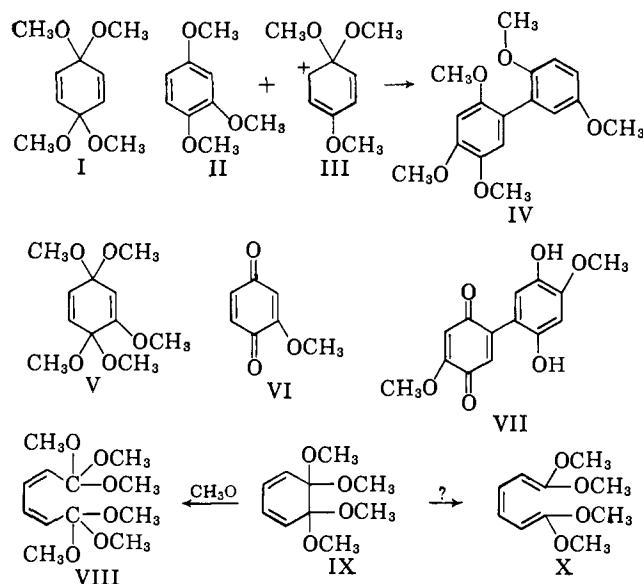
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**Electrochemical Syntheses. The Methoxylation of Dimethoxybenzenes to Quinone Ketals and the Ring Fission of 1,2-Dimethoxybenzene to Hexamethyl *cis,cis*-Orthomuconate<sup>1</sup>**

Sir:

With the exception of the Kolbe reaction<sup>2</sup> and various oxidation and reduction reactions which have found wide synthetic utility, very few explorations of the application of electrochemical methods to organic synthesis have been reported. The subject has been reviewed by Allen.<sup>3</sup> Recently, Corey, *et al.*,<sup>4</sup> have described an electrochemical method for the generation of carbonium ion from acids whereas Clauson-Kaas and



Elming<sup>5</sup> developed a method for the electrochemical methoxylation of furans. It is the purpose of this communication to report on the electrochemical methoxylation of the isomeric dimethoxybenzenes to quinone ketals, a novel class of quinone derivatives which have thus far remained inaccessible by classical routes.<sup>6</sup> In addition, we wish to report on a novel type of reaction which consists in the methoxylation accompanied by fission of veratrole to hexamethyl *cis,cis*-orthomuconate (VIII), an unusual substance of intriguing synthetic potentialities.

The electrolysis cell consisted of two platinum gauze anodes with a total surface area of 160 cm.<sup>2</sup> and a

nickel cathode with a surface area of 240 cm.<sup>2</sup> The two anodes were arranged concentrically about the cathode. The all-glass container was provided with a cold finger for internal cooling. Stirring was maintained magnetically during the course of all reactions. The source of direct current consisted in a conventional 6-2-v. battery charger connected to a variable transformer. The current was kept approximately constant by manually adjusting the transformer; in general, the applied current was in the range of 2 to 4 amp. All reactions were carried out at or below room temperature (−10 to 25°). The anodic current density was approximately 0.025 amp./cm.<sup>2</sup> In general, a two- or threefold excess of current equivalents was applied. A 1% methanolic potassium hydroxide solution was used as the solvent; the substrate concentrations were kept in the range of 10%. Under these conditions, electrolysis at 0° of 0.1 mole of hydroquinone dimethyl ether (2.0 amp., 3.6–3.8 v., 3 hr.) gave 3,3,6,6-tetramethoxy-1,4-cyclohexadiene (*p*-benzoquinone tetramethyl ketal) (I) in 75% yield,<sup>7</sup> m.p. 42.5°. *Anal.* Calcd. for C<sub>10</sub>H<sub>16</sub>O: C, 59.98; H, 8.05. Found: C, 60.18, H, 7.89. The n.m.r. spectrum<sup>8</sup> (CCl<sub>4</sub> as solvent) showed peaks at 6.75 and 4.02  $\tau$ ; the peak areas were in the ratio of 3:1 in agreement with the structure. An aqueous solution of the ketal deposits *p*-benzoquinone in quantitative yield when treated with a trace of mineral acid. Treatment of a 20% solution of I in dry benzene with one drop of boron trifluoride etherate (exothermic reaction) gives a mixture of 1,2,4-trimethoxybenzene (II) and a pentamethoxybiphenyl<sup>9</sup> (IV), m.p. 112–113.5° [*Anal.* Calcd. for C<sub>17</sub>H<sub>24</sub>O<sub>5</sub>: C, 67.09; H, 6.62; mol. wt., 304. Found: C, 66.34; H, 6.35; mol. wt., 347 (Rast)] in 36% and 19% yields, respectively. Similar treatment of a more dilute solution (10%) of I in benzene produces II and IV in 81 and 12% yields, respectively, thus suggesting the cation III as a common intermediate in these reactions. A simple route to certain polymethoxybiphenols therefore is provided.

Electrochemical methoxylation (at 0°, 4.5 amp., 7.5–7.9 v., 10 hr.) of resorcinol dimethyl ether (0.1 mole) also proceeded smoothly to give 2,3,3,6,6-pentamethoxy-1,4-cyclohexadiene (V) in 61% yield, b.p. 105–110° (3 mm.), *n*<sub>D</sub><sup>20</sup> 1.4750. *Anal.* Calcd. for C<sub>11</sub>H<sub>18</sub>O<sub>5</sub>: C, 57.58; H, 7.88. Found: C, 56.84; H, 7.89. The n.m.r. spectrum (in CCl<sub>4</sub>) showed peaks at 6.80 and 6.38  $\tau$  and a group of 8 peaks (identified as an ABX system) extending from 5.12 to 3.93  $\tau$ ; the relative areas of the two characteristic regions were in the ratio of 4:1 in agreement with the structure. In dilute aqueous acid, it was converted in high yield to the intensely blue biphenyl quinhydrone (VII) by way of methoxy-*p*-benzoquinone (VI) which has been shown<sup>10,11</sup> to couple to VII under acid conditions. Direct comparison (mixture m.p., infrared spectra) with an authentic specimen of VII prepared by the published procedure<sup>10,11</sup> served to establish the identity of the acid hydrolysis product of the ketal V. The structure of the latter was confirmed by an alternative electrochemical synthesis (at 10°, 4.0 amp., 6–6.6 v., 2.5 hr.) from 1,2,4-trimethoxybenzene (0.05 mole) (II) which afforded in 89% yield a ketal (V) identical in every respect with the one derived from resorcinol dimethyl ether.

(7) The current efficiency was calculated to be 66%. An 88% yield resulted when a fivefold increase in current was applied.

(8) Determined at 60 Mc./sec. with a Varian-V-4302 spectrometer.

(9) Structure IV is inferred. When the ketal is similarly treated but in 1,2,4-trimethoxybenzene as the solvent, the diphenyl (IV) is the major product as would be expected.

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(1) This investigation was supported by a grant from the National Cancer Institute of Canada.

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