By the same general method, 16-hydroxymethylene-3-ethylenedioxy-5-androsten-17-one [m.p. 203–206°; $(\alpha)_D$ +26.8°], prepared from 3-ethylenedioxy-5-androsten-17-one,[16] gave the corresponding 16 ξ-cyano derivative [m.p. 240–242°; $(\alpha)_D$ +4.3° (±21°, *c* 0.23)] which was converted to 16ξ-cyanotestosterone [m.p. 218–219°; $(\alpha)_D$ +88.5°; λ_{max} 240 mμ (ε 16,170)] by lithium borohydride reduction and acid-catalyzed removal of the ring-A blocking group. 16-Hydroxymethyleneestrone 3-methyl ether[17] and I yielded 16ξ-cyanosterone 3-methyl ether [m.p. 138–148°; $(\alpha)_D$ +189°] which on subsequent reduction with lithium borohydride afforded 16ξ-cyanoestradiol 3-methyl ether [m.p. 197–200°; $(\alpha)_D$ +54°].

The results of the as yet incomplete biological evaluation of these compounds will be reported in a forthcoming paper. No outstanding endocrinological activities have been discovered thus far.

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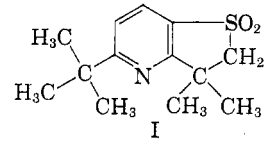
Reactivity of 2,6-Di-*t*-butylpyridine Toward Sulfur Trioxide at Elevated Temperature

Sir:

It has been known for several years that 2,6-di-*t*-butylpyridine can be sulfonated with sulfur trioxide at low temperature.[1] In an extensive investigation of the reactivity of 2,6-dialkylpyridines one of us (v. d. Pl.), together with den Hertog, has shown that during this reaction the sulfonic acid group entered the 3-position,[2–4] as in the sulfonation of pyridine below 300°. Since sulfonation of pyridine above 300° leads to the formation of pyridine-4-sulfonic acid and 4-hydroxypyridine, together with the 3-sulfonic acid,[5] we also studied the behaviour of 2,6-di-*t*-butylpyridine toward sulfur trioxide at elevated temperatures.

When 2,6-di-*t*-butylpyridine was heated with sulfur trioxide at 240–250° for fifteen hours in a sealed tube, neither 2,6-di-*t*-butylpyridine-4-sulfonic acid nor 2,6-di-*t*-butylpyridone-4 was formed. Instead, together with unchanged 2,6-di-*t*-butylpyridine (30–35%) and the 3-sulfonic acid (30–35%), a compound was isolated (15–20%) melting at 140–141°. It was insoluble in water but easily soluble in ether and ethanol. From elemental analysis and molecular weight determination its composition was established as $C_{13}H_{19}NO_2S$. *Anal.* Calcd. for $C_{13}H_{19}NO_2S$: C, 61.62; H, 7.56; N, 5.53; S, 12.66; mol. wt. 253. Found: C, 61.9; H, 7.4; N, 5.5; S, 12.1; mol. wt. (according to Rast) 245. Taking into account its composition, mode of formation and the fact that the compound could not be hydrolyzed in an alkaline medium, it was considered to be best represented by structure I,[4] 2,3-dihydro-3,3-dimethyl-5-*t*-butylthieno[3,2-*b*]pyridine 1-dioxide.



I

We now wish to report that this conclusion was correct. The infrared spectrum of I in chloroform shows two strong bands at 1134 cm.$^{-1}$ and 1316 cm.$^{-1}$, both indicating the presence of a sulfone group in the molecule.[6] That no rearrangement of the *t*-butyl group occurred during heating of the 2,6-di-*t*-butylpyridine with sulfur trioxide was established by considering the NMR spectrum of I (internal reference tetramethylsilane, solvent tetrachloromethane, 60 mc., magnetic field approximately 14,100 gauss). In this spectrum two peaks were observed with τ-values,[7] 2.38 and 2.88, both peaks being characterized by doublet structures with coupling constants J = 8 c.p.s. The τ-values agree with those given for the β- and γ-protons of the pyridine nucleus.[8] The coupling constants, J = 8 c.p.s. also affirm the presence of both β- and γ-protons in the pyridine nucleus, being in good agreement with $J_{\beta\gamma}$ = 7.35 c.p.s. given for 2,3-substituted pyridines.[9] These data exclude the possibility of an α-proton being present in the pyridine nucleus. Further, the NMR spectrum shows peaks at τ-values 6.74, 8.45, and 8.63, attributed, respectively, to the proton resonance peaks of the methylene-, the two methyl groups, and the *t*-butyl group. The intensity ratio of these three peaks, 2:6.1:9, supports these assignments. The paramagnetic shift of the protons of the methylene group is due to the deshielding by the adjacent electron-withdrawing sulfone group.

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The infrared and the NMR data thus provide strong evidence for structure I. The peculiar formation of a substituted dihydro-thiophene ring from a reaction of sulfur trioxide on an alkylated aromatic compound has not previously been reported and an investigation of the mechanism of this reaction and its applicability to other compounds is being continued.

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Aqueous Mesitoate Electrolysis, Kolbe-Inhibited[1]

Sir:

We wish to report that the aqueous potassium 2,4,6-trimethylbenzoate fails to give typical Kolbe products on electrolysis.[2] This failure will be termed Kolbe inhibition.

Kolbe inhibition is more common in water than in organic solvents and the feature of inhibition in water is the production of oxygen with, sometimes, oxidative degradation. Certain features of structure encourage inhibition such as the presence of a double bond, a cycloalkyl group or an aromatic ring[3] near the carboxyl group.

If the published[4] mechanism is correct then benzenoid inhibition can be explained by an electron deficiency at the carboxyl group. However, Hammett and Treffers[5] showed that when benzoic acid is compared with mesitoic acid as the solute in pure sulfuric acid for freezing point lowering at high dilution, benzoic acid acquires a proton from the solvent to form two particles for every molecule of benzoic acid, while mesitoic acid gives hydroxide ion to the solvent to form four particles for every molecule of mesitoic acid. Presumably, the electron concentration at the carboxylate end of mesitoic acid could be due to the electron donation by *ortho-para* methyls, transmitted by resonance through the benzene ring. Thus, it seems possible that electrons could be withdrawn from the mesitoate ion at the anode to give the Kolbe reaction. Attempted Kolbe electrolysis of potassium mesitoate in water showed that during the course of reaction measurable amounts of carbon dioxide appeared in the anode gas. The electrolyte turned dark with no oil or solid separating, except a minute amount of yellow ether-insoluble material judged polymeric. Absence of other insoluble material negates the formation of any hydrocarbons RR, (R minus H), or mesityl mesitoate, RCOOR. As ROH is a frequent Kolbe product, mesitol was sought in the dark electrolyte. Conventional organic qualitative chemical analysis yielded negative results.

According to Porter and Thurber,[6] mesitol is oxidized by silver oxide to give a quinone free radical of the mesitol, which by proton bonding with a molecule of mesitol gives an analogue of quinhydrone. It is conceivable that the electrolysis of mesitoic acid should yield such a quinhydrone-type organic compound by anodic oxidation if ArOH is present.

Isolation of this compound was attempted without success. Polarographic analysis shows no similarity between the chemically oxidized and the electrolyzed compounds.

We therefore conclude that ring-rupture by anodic oxidation accounts for the carbon dioxide and polymer, and that mesitoic acid is aromatic-inhibited in water. We hypothesize that either carboxylate electron congestion does not occur upon this acid in aqueous solution, or that electron unavailability at the carboxyl is not the cause of benzenoid inhibition. The former idea is supported by the fact that the ionization constant of mesitoic acid is not much lower than that of benzoic acid, both in water at 25°; methyl electron-donation should reduce extent of proton loss. Steric hindrance to carboxyl-and-ring planarity can reasonably account for the lack of electronic transmission, but requires a different explanation for the Hammett[5] results. Perhaps the steric hindrance would tend to push off the hydroxyl group but at the same time prevent the carboxylate ion from getting close to the anode.

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