

verted to a stable transannular peroxide^{23,24} which was isolated, characterized, and identified as the 5,8-peroxide of $\Delta^{5,7,24}$ -cholestatrien-3 β -ol, m.p. 138–139°, $[\alpha]_D -4.3^\circ$ (CHCl₃), $[\phi] -18^{25}$; n.m.r., τ 9.10, 9.17 (C-18, C-19, and C-21 methyls); 8.28, 8.36 (C-25 vinyl methyls); 3.51, 3.80 (C-6 and C-7 vinyl protons); 4.96 (C-24 vinyl proton). *Anal.* Found: C, 77.93; H, 10.17, in agreement with C₂₇H₄₂O₃. Structure was adduced by hydrogenation with PtO₂ as catalyst to the cholestane-3 β ,5 α ,8 α -triol (III, R = H),²⁶ m.p. 185–187°, $[\alpha]_D -21.4^\circ$ (pyridine), $[\phi] -88$. *Anal.* Found: C, 77.20; H, 11.43, in agreement with C₂₇H₄₈O₃. The triol (III) proved to be identical with an authentic sample prepared from II by photosensitized transannular addition of oxygen²³ followed by hydrogenation.

Our findings reflect the role of 7-dehydrocholesterol as intermediate on the major pathway of hepatic cholesterol synthesis⁶ and indicate that $\Delta^{5,7,24}$ -cholestatrien-3 β -ol (I) is a precursor of 7-dehydrocholesterol and of 24-dehydrocholesterol and is not a metabolite of the latter.³¹ However, the quantitative importance of I as an obligatory intermediate on the normal pathway of cholesterol biosynthesis depends on the degree of side-chain reduction occurring at any one point in the normal pathway.⁴

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(22) Attempts to isolate pure I from livers of 30 rats treated with triparanol and AY-9944 were not successful. However, gas-liquid chromatography of the hydrolyzed neutral fraction indicated the presence of a peak with retention time corresponding to that calculated for I by the method of R. B. Clayton, *Biochemistry*, **1**, 357 (1962). This finding lends support to the recent report on the probable presence of I in rat liver homogenates [M. E. Dempsey, J. D. Seaton, M. G. Sanford, and R. W. Trockman, *Federation Proc.*, **23**, 425 (1964)].

(23) F. Schenck, K. Buchholz, and O. Wiese, *Ber.*, **69**, 2696 (1936). The peroxide (0.8 g.) was separated from cholesterol by chromatography on florisil and purified by "thick" layer chromatography.

(24) It is interesting to note that the same procedure, applied to the brain of the same pig, has led to the isolation of the peroxide of II, thus suggesting inability of triparanol to cross the blood-brain barrier.

(25) Molecular rotation [*cf.* P. M. Jones and W. Klyne, *J. Chem. Soc.*, 871 (1960)].

(26) The corresponding acetate (III, R = CH₃CO) exhibited m.p. 160–162°, $[\alpha]_D -41.2^\circ$ (CHCl₃), $[\phi] -190$; n.m.r., τ 4.96 (carbinolic proton). *Anal.* Found: C, 75.09; H, 10.81, in agreement with C₂₇H₄₀O₄.

DEPARTMENT OF BIOCHEMISTRY
AYERST RESEARCH LABORATORIES
MONTREAL, CANADA

D. DVORNIK
M. KRAML
J. F. BAGLI

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The Vertical Ionization Potentials of Phenyl and Phenoxy Radicals

Sir:

Recent measurements¹ of the appearance potentials of C₆H₅⁺ ions from phenyl halides lead to $\Delta H_f(\text{C}_6\text{H}_5^+) = 288$ kcal./mole. This value is significantly lower than earlier values of ~ 300 kcal./mole given by the appearance potentials of C₆H₅⁺ ions from benzene and toluene^{2–4} and phenyl halides.⁴ From $\Delta H_f(\text{C}_6\text{H}_6) = 70$ kcal./mole^{5,6} and $\Delta H_f(\text{C}_6\text{H}_5^+) = 288$ kcal./mole Majer and Patrick obtained 9.4 v. for the ionization

potential of the phenyl radical. This result is much lower than earlier values of $I(\text{C}_6\text{H}_5) = 9.9$ v.^{2–4} based on $\Delta H_f(\text{C}_6\text{H}_5^+) = 300$ kcal./mole, and is close to the ionization potential of benzene itself, 9.25 v.^{7,8}

The vertical ionization potential of the phenyl radical has been recently measured in this laboratory by electron impact ionization of phenyl radicals generated by the thermal decomposition of azobenzene at 800° in a reactor coupled to a mass spectrometer. In addition to the phenyl radical, benzene and biphenyl were produced. The apparatus and the method of evaluating the vertical ionization potential by comparison with a rare gas standard have been described.⁹ The average of six determinations gives $I_{\text{vert}}(\text{C}_6\text{H}_5) = 9.20$ v., in reasonable agreement with Majer and Patrick's value.¹ $I_{\text{vert}}(\text{C}_6\text{H}_6)$ measured in the same apparatus was 9.50 v., *i.e.*, 0.25 v. higher than the adiabatic value.⁷ Since it may reasonably be expected that the adiabatic ionization potential of phenyl radical will be lower than the vertical value of 9.2 v. by a roughly similar amount, it appears that $I(\text{C}_6\text{H}_5)$ is less than $I(\text{C}_6\text{H}_6)$ by about 0.3 v.

An upper limit for $\Delta H_f(\text{C}_6\text{H}_5^+)$ can be obtained from the present result, using the relationship

$$\Delta H_f(\text{C}_6\text{H}_5^+) \leq I_{\text{vert}}(\text{C}_6\text{H}_5) + \Delta H_f(\text{C}_6\text{H}_6)$$

Although $\Delta H_f(\text{C}_6\text{H}_5)$ is generally taken at 70 kcal./mole^{5,6} the bond stretching frequency in benzene suggests a slightly higher value, 73 kcal./mole.¹⁰ Taking this value and $I_{\text{vert}}(\text{C}_6\text{H}_5) = 9.20$ v. (212 kcal./mole), $\Delta H_f(\text{C}_6\text{H}_5^+) \leq 285$ kcal./mole, in close agreement with Majer and Patrick's value of 288 kcal./mole (which is also an upper limit). This result clearly shows that the appearance potentials for C₆H₅⁺ ions from aromatic hydrocarbons include considerable excitational energy. This is consistent with labeling experiments¹¹ which show that the formation of C₆H₅⁺ ions from toluene and other aromatic hydrocarbons is accompanied by extensive reshuffling of H atoms, and perhaps even the loss of the phenyl structure. On the other hand, the agreement of the upper limit for $\Delta H_f(\text{C}_6\text{H}_5^+)$ derived from the present result with that obtained from the dissociative ionization of phenyl halides¹ indicates that C₆H₅⁺ ions from phenyl halides have probably retained the phenyl configuration.

The measurement of the vertical ionization potential of the phenoxy radical C₆H₅O was carried out in the same apparatus. The radicals were produced by the thermal decomposition of allyl phenyl ether. The phenoxy radical has previously been detected by flash photolysis in absorption¹² and in the thermal decomposition of anisole by mass spectrometry.¹³ In the thermal decomposition of allyl phenyl ether, which decomposes at a much lower temperature than anisole, a good yield of phenoxy radicals was obtained. Comparison of the ionization efficiency curve for phenoxy radical (mass 93) with that of a Kr standard gave

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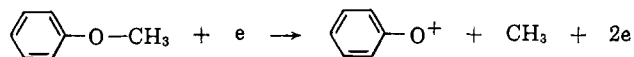
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(6) M. Szwarc, *Chem. Rev.*, **47**, 75 (1950).

8.84 v. for $I_{\text{vert}}(\text{C}_6\text{H}_5\text{O})$. As would be expected, this is considerably higher than the ionization potential of the isoelectronic benzyl radical (7.76 v.).¹⁴ The appearance potential of the $\text{C}_6\text{H}_5\text{O}^+$ fragment ion from anisole was found to be 11.92 ± 0.1 v., in good agreement with the value obtained by Harrison, *et al.*¹⁵ Assuming this process to be a simple bond rupture in



which the structural identity of the $\text{C}_6\text{H}_5\text{O}$ fragment is preserved, the relationship $D(\text{R}-\text{Y}) \leq A(\text{R}^+) - I(\text{R})$ gives $D(\text{C}_6\text{H}_5\text{O}-\text{CH}_3) \leq 71$ kcal./mole. Evidence for the retention of the phenoxy structure in $\text{C}_6\text{H}_5\text{O}^+$ ions from anisole at the dissociation threshold is provided by the results of Harrison, *et al.*, who found *meta-para* orientation to be preserved in $\text{RC}_6\text{H}_4\text{O}^+$ ions produced in the dissociative ionization of $\text{RC}_6\text{H}_4\text{OCH}_3$ isomers. One might reasonably expect the O- CH_3 bond in anisole to be appreciably lower than this limit, however. The phenoxy radical is isoelectronic with benzyl radical, and should therefore exhibit considerable resonance stabilization. To a very rough approximation, then, $D(\text{CH}_3\text{O}-\text{CH}_3) - D(\text{C}_6\text{H}_5\text{O}-\text{CH}_3) \approx D(\text{CH}_3-\text{CH}_3) - D(\text{C}_6\text{H}_5\text{CH}_2-\text{CH}_3)$. Taking $\Delta H_f(\text{CH}_3) = 32.5$ kcal./mole¹⁶ and $\Delta H_f(\text{C}_6\text{H}_5\text{CH}_2) \sim 43$ kcal./mole,¹⁷ and the standard heats of formation of ethane and ethylbenzene,¹⁸ $D(\text{CH}_3-\text{CH}_3) - D(\text{C}_6\text{H}_5\text{CH}_2-\text{CH}_3) \sim 17$ kcal./mole.

If $D(\text{CH}_3\text{O}-\text{CH}_3) = 77$ kcal./mole,¹⁹ then $D(\text{C}_6\text{H}_5\text{O}-\text{CH}_3) \approx 60$ kcal./mole. On this basis, the appearance potential of $\text{C}_6\text{H}_5\text{O}^+$ from anisole would include 11 kcal./mole of excitational energy. The validity of such a comparison is rather doubtful, however. Other phenoxy derivatives (phenol, phenyl ethyl ether, diphenyl ether) have such small intensities for $\text{C}_6\text{H}_5\text{O}^+$ ion that estimates of $\Delta H_f(\text{C}_6\text{H}_5\text{O}^+)$ cannot be made from them. The value given above for $A(\text{C}_6\text{H}_5\text{O}^+)$, together with $\Delta H_f(\text{anisole}) = -18.5$ kcal./mole, leads to $\Delta H_f(\text{C}_6\text{H}_5\text{O}^+) \leq 224$ kcal./mole and $\Delta H_f(\text{C}_6\text{H}_5\text{O}) \leq 20$ kcal./mole. Probable lower limits would appear to be about 10 kcal./mole less.

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(20) Issued as N. R. C. No. 8041.

DIVISION OF PURE CHEMISTRY
NATIONAL RESEARCH COUNCIL²⁰
OTTAWA, CANADA

I. P. FISHER
T. F. PALMER
F. P. LOSSING

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Dependency of Vicinal Coupling Constants on the Configuration of Electronegative Substituents

Sir:

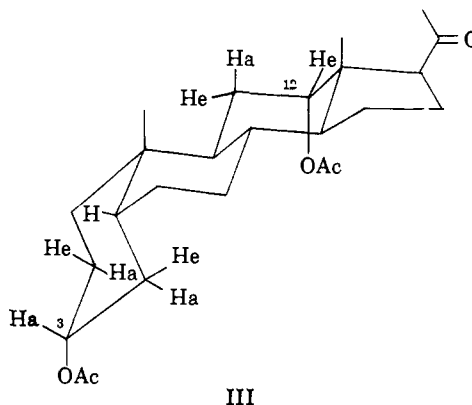
Recently, a number of studies have illustrated the decrease in vicinal coupling constants in saturated (I) or unsaturated (II) systems on increasing the electronegativity of a substituent (R) attached to the same

carbon atom as one of the vicinally coupled protons.¹ In vinyl compounds (II) it has been demonstrated that the *cis*-vicinal coupling constant ($J_{\text{HH}'}$) is more sensitive than the *trans*-vicinal coupling constant ($J_{\text{HH}''}$) to the electronegativity of R,^{1c} in qualitative agreement with the theoretical requirements.²



However, the variation of vicinal coupling constants with the *orientation* of a given electronegative substituent in saturated systems (I) has been virtually neglected. We have at present evidence which suggests that such variations are quite large in the fundamentally important chair form of a cyclohexane ring.

In the downfield region of the 60 Mc. n.m.r. spectrum of 5 β -pregnane-3 α ,12 α -diol-20-one diacetate (III), obtained in benzene solution, the resonance of the axial 3 β -proton appears as a seven line pattern centered at δ 4.77 p.p.m., while the equatorial 12 β -proton signal is evident as a triplet centered at δ 5.12 p.p.m.³ The seven line pattern is observed because the two diaxial splittings to the 2 α - and 4 α -protons (10 c.p.s.) are twice the two axial-equatorial splittings to the 2 β - and 4 β -protons (5 c.p.s.). Evidently, the equatorial 12 β -proton approximately bisects the angle between the C-11 methylene protons and the equatorial-axial splitting is equal to the diequatorial splitting (2.5 c.p.s.).



Since there is no obvious reason why both rings A and C in III should not exist in normal chair forms, we felt that the large difference between the axial-equatorial splittings associated with the 3 β - and 12 β -protons, involving very similar dihedral angles (60°), might arise through the differing configuration of the acetate groups (equatorial and axial, respectively). To test this hypothesis we determined the spectra of a number of other steroids containing acetate functions in rings A and C. Since the hydroxyl group is similar in electronegativity to the acetate function,^{1a} its effect was anticipated to be similar and a number of hydroxy steroids were also examined. All spectra were

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(3) The resonance position of a proton on the δ scale is related to the frequency (ν) such that δ (p.p.m.) = $\nu/60$ in the 60 Mc. spectrum, when the frequency of the tetramethylsilane reference is arbitrarily taken as zero.