acetone (freshly distilled from potassium permanganate) under a nitrogen atmosphere was added 5.7 ml. of chromic acid solution[11] (26.72 g. of chromium trioxide in 23 ml. of concentrated sulfuric acid diluted to 100 ml. with water) over 1 min. with stirring. After an additional 3 min. of stirring, the mixture was poured into 10 l. of ice–water and filtered. The solid product was dried in a vacuum desiccator overnight, dissolved in methylene chloride, filtered, and evaporated to dryness in the cold to yield 3.18 g. of white solid. The infrared spectrum of this material in carbon disulfide solution showed carbonyl absorption at 1709 cm.$^{-1}$ (20-ketone) and 1718 cm.$^{-1}$ (sh) (3-ketone) as well as absorption bands consistent with the presence of a benzyl ether grouping and weak hydroxyl absorption. The carbonyl absorptions of another sample in a potassium bromide pellet were at 1711 and 1693 cm.$^{-1}$. The remainder of the product was carried to the next step without additional purification by solution in 500 ml. of redistilled 95% ethanol and shaking with hydrogen in the presence of several grams of W-2 Raney nickel at room temperature and atmospheric pressure. The reaction mixture was filtered and solvent removed. The product was triturated with a small volume of ether. The ether-insoluble material (1.54 g.) had a strong carbonyl absorption band at 1706 cm.$^{-1}$ in carbon disulfide solution and was presumably a mixture of 3α + β,16α-dihydroxy-Δ^5-pregnen-20-one (L). Since the desired isomeric Δ^5-pregnene-3,16α,20-triols could be separated readily, no attempts at fractionation of the 3α- and 3β-hydroxy epimers of L were made.

Crude L (1.5 g.) was dissolved in a minimum amount of freshly distilled tetrahydrofuran and added to an excess of lithium aluminum hydride in ether. The reaction mixture was allowed to stand at room temperature for 40 hr. and then worked up in the usual fashion. The solid product was triturated with a small volume of ether and the residual solid (1.37 g.) was treated with 6 g. of digitonin in 100 ml. of 90% ethanol. This was allowed to stand at room temperature overnight and extracted with ethyl acetate. The solvent was removed and 872 mg. of crude "α-fraction" was obtained. The insoluble digitonide was dissolved in 35 ml. of pyridine, diluted with 2 l. of ethyl acetate, and filtered. The filtrate was washed with 10% hydrochloric acid, water, sodium bicarbonate solution, and finally with water, dried over anhydrous sodium sulfate, and distilled to give 500 mg. of crude "β-fraction."

The "β-fraction" was chromatographed on 175 g. of silica gel containing 70 ml. of ethanol on the stationary phase. Elution with 6% ethanol in methylene chloride yielded 110 mg. of Δ^5-pregnene-3β,16α,20α-triol (Ea) which melted at 243.5–245.5° after recrystallization from methanol. Further elution with 6% and 8% ethanol in methylene chloride gave 270 mg. of Δ^5-pregnene-3β,16α,20β-triol (D), m.p. 268, 280–287°; the infrared spectrum in potassium bromide dispersion was identical with that of D obtained in the previous synthesis. The sample was free of impurity as judged by thin layer chromatography on silica gel G with ethyl acetate.

The "α-fraction" was chromatographed on 150 g. of silica gel and 60 ml. of ethanol. Elution with 4% ethanol in methylene chloride gave 83 mg. of **Δ^5-pregnene-3α,16α,20α-triol (Ha)** which melted at 229.5–230° after recrystallization from ethanol. The infrared spectrum in a potassium bromide dispersion was identical in all respects with that of the triol from natural sources. Acetylation with acetic anhydride and pyridine yielded the triacetate Hb, m.p. 136–137°, after recrystallization from methanol. The triacetate prepared from the urinary triol had m.p. 133–135°; m.m.p. was 137–139°. The infrared spectra of the two samples were identical in all respects in carbon disulfide solution.

Elution with 5% ethanol in methylene chloride gave 355 mg. of fractions containing Δ^5-pregnene-3α,16α,20β-triol (M), m.p. 224–225°, after recrystallization from methanol; $[\alpha]^{27}\text{D}$ −94.3° (ethanol); $\nu_{\max}^{\text{KBr}}$ 3530 (sh), 3460, 3390, 1663, 1086, 1064, 1049, 1020, 881, 867, 804 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.23; H, 10.15.

The **triacetate** was prepared by the action of acetic anhydride in pyridine and melted at 137.5–140° after several recrystallizations from methanol; $[\alpha]^{26}\text{D}$ −81.6°; $\nu_{\max}^{\text{CS}_2,\ \text{CCl}_4}$ 1738, 1667, 1239, 1158–1151 (sh), 1046, 1035, 1020 cm.$^{-1}$. Further elution with 5% ethanol in methylene chloride gave small amounts of Δ^5-pregnene-3β,16α,20β-triol (D) identical with that isolated from the β-fraction.

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Secondary Hydrogen Isotope Effects on Deoxymercuration[1]

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Secondary isotope effects on the rate of acid-induced deoxymercuration of 2-phenyl-2-methoxyethylmercuric iodide have been studied. Deuterium substitution at the 2-carbon gives k_H/k_D, 1.12. Deuterium substitution at the 1-carbon gives k_H/k_D, 0.91. The latter is one of a small number of inverse isotope effects that have been observed. From these and results previously presented it is concluded that the deoxymercuration transition state has a partial positive charge on the carbon from which oxygen is leaving and also has some olefin–mercuric iodide complex character.

In a previous paper[2] the acid-induced deoxymercuration rate for $CH_3OCD_2CD_2HgI$ (II) was compared with that for $CH_3OCH_2CH_2HgI$ (I). They were very similar (k_H/k_D = 1.06), and from this it was concluded that the transition state must resemble the protonated starting state, IX. More recent studies of relative reactivities[3] indicate that this view was oversimplified. It was shown that either the carbonium ion, VII, or the olefin mercuric iodide complex, VIII, or both, must contribute to the transition state electronic structure. The present paper describes further work on secondary hydrogen isotope effects, involving isotopic substitution in $C_6H_5CH(OCH_3)CH_2HgI$ (III) designed to shed more light on the electronic structure of the transition state and to explain the apparent discrepancy between the results obtained from the secondary isotope effect and those obtained from the effect of substitution.

Results

Well established synthetic methods were used to prepare III, $C_6H_5CD(OCH_3)CH_2HgI$ (IV), C_6H_5-$CH(OCH_3)CD_2HgI$ (V), and $C_6H_5CD(OCH_3)CD_2HgI$ (VI). Acid-induced deoxymercuration rates were

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[1] This work was supported by the Air Force Office of Scientific Research through contract no. AF 49(638)711. Reproduction in whole or in part is permitted for any purpose of the U. S. Government.

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measured for all of these in water containing 2% of methanol at 25.0°. First-order rate constants were evaluated spectrophotometrically in the usual way.[2] The acid was provided by acetic acid–sodium acetate buffers. Second-order rate constants, k, were obtained by dividing the first-order rate constants by the hydronium ion concentration. Ratios of rates were evaluated by comparing rates obtained from solutions that were made up from the same buffers and were run in the cell block at the same time, so that there would be no possibility of temperature or buffer discrepancies. Table I reports the mean of the various second-order rate constants, the probable error of each rate constant,[4] the ratio of k_{III} to each k, and the probable error of each ratio, as estimated from the average deviation from the mean of ratios of rate constants obtained simultaneously. Each reported mean value was obtained from four to six individual determinations.

TABLE I

KINETIC ISOTOPE EFFECTS IN THE DEOXYMERCURATION OF $C_6H_5CH(OCH_3)CH_2HgI$

Compound	k	Δk	k_{III}/k	$\Delta(k_{III}/k)$
III	12.16	0.08		
IV	11.03	.10	1.12	0.02
V	13.62	.13	0.91	.02
VI	11.50	.07	1.07	.02

In addition to random errors in measuring, rates k_{IV} may be a little high and k_{III}/k_{IV} a little low (each by a factor of 1.02) due to isotopic contamination. This is discussed in the Experimental.

It is not strictly required by theory that k_{III}/k_{VI} should be exactly given by the product of k_{III}/k_{IV} and k_{III}/k_V, but in other cases[5–7] where the data is sufficiently extensive such a product relationship has been found to hold approximately. Such a relationship is in accord with the rule of the geometric mean.[8] It is, therefore, reassuring that the present data does conform to such a pattern within the combined experimental uncertainties.

Spectroscopic Results.—Infrared spectra were made using a Perkin-Elmer Model 421 infrared spectrophotometer of thin liquid films of compounds III–VI. These serve to identify the stretching frequencies associated with the methylene and methine groups, but a complete experimental assignment of frequencies for molecules of this complexity is beyond our present capacity. The stretching frequencies are shown in Table II.

TABLE II

ALIPHATIC STRETCHING FREQUENCIES IN CM.$^{-1}$ FOR $C_6H_5CH(OCH_3)CH_2HgI$ AND ITS ISOTOPIC VARIANTS

Compound	Methine	Methylene (sym.)	Methylene (assym.)
III	2885	2910	2850
IV	2107	2910	2850
V	2885	2231	2138
VI	2107	2231	2138

Discussion

The results of isotopic substitution at the hydrogen α to the methoxy group is in good accord with data for other reactions whose rate-determining steps produce carbonium ions or related species.[5,6,9,10] Values of k_H/k_D are generally in the range 1.10 to 1.20 per isotopic substitution, and the present value falls well within that range. Such isotope effects have been attributed primarily to a lowering of one of the bending frequencies in the transition state,[5] and there is no reason to question that interpretation in the present case.

Inverse secondary hydrogen isotope effects are not without precedent,[11,12] although they seem to be fairly rare. The effect observed on deuterium substitution in the methylene group may be the result of an alteration of vibrational frequencies toward those appropriate to the olefin–mercuric ioide π-complex in the transition state. It previously has been pointed out that such a change would probably lead to an inverse isotope effect.[2]

It should be pointed out that both the previous prediction and the present results (for substitution in the methylene group) imply that it is possible to progress toward sp^2 hybridization from sp^3 hybridization with $k_H/k_D < 1.0$ at the carbon atom undergoing the change. Since this takes place without the intervention of a new incoming group, it is contrary to a previous suggestion that such changes should always $k_H/k_D > 1.0$.[5,13,14] It must be admitted, however, that deoxymercuration involves rather special structures and may be a special case. The reported stretchin frequencies show no anomalies, which suggests that the origin of the effect is not in the starting state.

It now seems likely that the very small isotope effect previously observed[2] was due to an approximate cancellation of two effects of opposite sign, rather than to a transition state closely resembling the starting state, as was previously assumed. This, of course, resolves the apparent conflict between the conclusions previously based on the isotope effect and those based on relative reactivity[3] in favor of the latter. There is a substantial charge deficit in the transition state at the carbon from which the methoxy group is leaving. In terms of resonance structures there are important contributions to the transition state from VII as well as from the protonated starting state, IX. The explanation given before for the effect of deuterium substitution in the methylene group would also require significant contributions from VIII, but there is no evidence for the participation of X. The significant participation of X would probably yield $k_H/k_D > 1.0$ for deuterium substitution in the methylene group.

It is interesting that the quantitative parallel between the present results and the earlier ones[2] is not too good.

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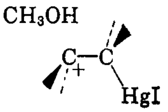
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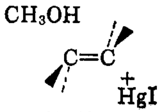
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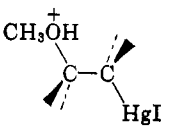
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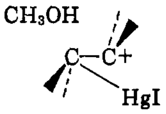
X

If it is assumed that double isotopic substitution at the hydrogens α to the methoxy group in I would contribute a factor $(k_{III}/k_{IV})^2$ to k_I/k_{II}, and that the isotopic substitution of the hydrogens α to the iodomercuri group would contribute a factor k_{III}/k_V, then k_I/k_{II} would be ~1.14. This probably should be multiplied by a further factor of 1.035 arising from the pre-exponential ratio of reduced masses[2] to give a calculated value of ~1.18 for k_I/k_{II}. Although still small this is considerably larger than the value, 1.06, actually found. These results support the suggestion that quantitative changes in the transition state electronic structure accompany the introduction of an alkyl group on the carbon atom bearing the methoxy group. These changes probably involve the incorporation of more carbonium ion character at that position. On the other hand it is possible that the lack of quantitative correspondence is due to the fortuitous accumulation of mechanical factors[15] and/or experimental errors and is without significance.

Experimental

All the isotopic versions of 2-phenyl-2-methoxyethylmercuric iodide were prepared from the corresponding styrenes by Schaleger's method,[3] and each had m.p. ~30°. In each case, the styrene was prepared from the corresponding 1-phenylethanol by the method of Berstein, Bennett, and Fields.[16]

An ethereal solution of 2.06 g. (0.0492 mole) of lithium aluminum deuteride (Metal Hydrides, 99.5%) was added slowly from a dropping funnel to 35.3 g. (0.294 mole) of acetophenone dissolved in 200 ml. of dry ether to give 1-deuterio-1-phenylethanol after 2 hr. of refluxing followed by hydrolysis with an ethanol-water mixture. The usual precautions to exclude water were observed prior to the hydrolysis. An excess of acetophenone was used, and the usual order of the addition was reversed in order to minimize the possibility of deuterium substitution at the 2-carbon.

In a similar manner 2,2,2-trideuterio-1-phenylethanol was prepared from trideuterioacetophenone and lithium aluminum hydride. The trideuterioacetophenone was prepared by shaking acetophenone with three successive portions of sodium deuteroxide in excess deuterium oxide. Each shaking was continued until the infrared spectrum of the acetophenone showed no further change. The first shaking required about 1 hr. and each of the others about 0.5 hr.

The 1,2,2,2-tetradeuterio-1-phenylethanol was prepared from trideuterioacetophenone and lithium aluminum deuteride in a similar fashion.

The 1-phenylethanols were converted to styrenes without purification or weighing. The over-all yields of styrene were around 18% based on the lithium aluminum hydride or deuteride which was the limiting reagent in each case. The styrenes each showed only one peak in vapor phase chromatography.

To estimate isotopic purity, n.m.r. spectra of compounds III–VI were obtained in carbon tetrachloride solution. Each of these showed an aromatic band at τ ~2.7 p.p.m. and a sharp singlet at τ 6.65 p.p.m., attributed to the methoxy group. In addition III showed a band with the appearance of a triplet centering at τ 7.56 p.p.m., and a second triplet, with about half the intensity of the first, centering at 5.20 p.p.m. The former is attributed to the methylene group, the two protons being nonequivalent[17] and each signal being split by the methine proton. If the central lines are unresolved, the band has the appearance of a triplet. The smaller triplet is attributed to the methine proton. Again a quartet is predicted but a triplet would result if the central lines were unresolved. In the spectrum of IV the larger triplet becomes, roughly, a doublet, and the smaller triplet all but disappears. From the residual intensity of the smaller triplet a minimum isotopic purity of 85% can be estimated. In the spectrum of V no trace of the larger triplet can be found, and the methine band appears as a single peak. Assuming that a peak twice the height of the noise would have been detected a minimum isotopic purity of 90% is estimated. Neither methylene nor methine signal can be detected in the spectrum of VI and with the same assumption about detectability 90% isotopic purity is again estimated. The latter two values indicate that k_{III}/k_V and k_{III}/k_{VI} given in Table I are not appreciably in error due to isotopic impurity. However it is possible that k_{III}/k_{IV} may be in error by as much as a factor of 1.02 due to isotopic contamination. None of the conclusions discussed previously would be altered by such an error. The n.m.r. spectra were obtained on a Varian Model 4311 high resolution spectrometer operating at 56 Mc. Tetramethylsilane was used as an internal reference.[18]

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