resonance peaks corresponding to the starting materials were replaced by new peaks with chemical shift of -7.1 ± 0.1 p.p.m., and light yellow solids were formed. These peaks are assigned to m- and p-fluoro-iodobenzene dichloride and were the only peaks observed in saturated solutions prepared by dissolving washed samples of the solids in carbon tetrachloride. The chlorine analyses of the solids showed 24.5% for the $para$ isomer and 23.5% for the $meta$ isomer, compared to a calculated value of 24.2%.

The nearly zero difference between the chemical shifts of the p- and m-dichlorides indicates a negligible resonance contribution to the reactivity constant, σ. This conclusion is based on Taft's rather precise correlation[15]

$$\int_{H}^{p\text{-}X} - \int_{H}^{m\text{-}X} = (-29.5)\sigma_R^0$$

where $\int_{H}^{p\text{-}X}$ and $\int_{H}^{m\text{-}X}$ are the fluorine chemical shift of p- and m-substituted fluorobenzenes, respectively, in p.p.m. (Table I) defined in the usual manner with respect to fluorobenzene. The substituent constant σ^0 is defined by Taft as the sum of σ_R^0 and σ_1, the resonance and inductive contributions, respectively, to the constant σ^0. His complementary correlation[15]

$$\int_{H}^{m\text{-}H} = -7.1\sigma_I + 0.60$$

predicts $\sigma_I = +1.1$. Then, on the basis of the equations

$$\sigma_p^0 = \sigma_I + \sigma_R^0$$

and

$$\sigma_m^0 = \sigma_I + 0.5\sigma_R^0 \ (para)$$

where σ_p^0 and σ_m^0 refer to $para$ and $meta$ substituents respectively, we estimate $\sigma_p^0 \cong \sigma_m^0 \cong \sigma_I \cong 1.1$. Similar conclusions can be drawn on the basis of Taft's alternative relationships[12]

$$-\int_{H}^{m\text{-}X} = 5.83\sigma_I - 0.2$$

and

$$-\int_{H}^{p\text{-}X} = 5.83\sigma_1 + 18.80\sigma_R - 0.8$$

where $\sigma \equiv \sigma_R + \sigma_I$. With the present data, these equations lead to a negligible σ_R-value and $\sigma_m \cong \sigma_p \cong \sigma_I \cong 1.3$ for the $-ICl_2$ substituent.

Thus, all our results indicate that the $-ICl_2$ functional group in aromatic molecules exerts a profound inductive effect of electron withdrawal and a negligible resonance effect. This inability to interact by resonance is consistent with the small effect which $para$ substituents have on the rates and equilibria for dissociation of derivatives of iodobenzene dichloride.[1]

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7-Quadricyclo[2.2.1.0^{2,6}0^{3,5}]heptanone
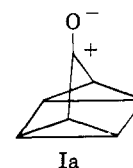## (Quadricyclanone)

Sir:

We wish to record the synthesis and some of the properties of a rather unusual tetracyclic ketone, 7-quadricyclo[2.2.1.0^{2,6}.0^{3,5}]heptanone (I). Oxidation of 7-quadricyclo[2.2.1.0^{2,6}.0^{3,5}]heptanol (II)[1] with t-butyl hypochlorite produces quadricyclanone (I) in 14% yield. The ketone (I) is reduced nearly quantitatively to quadricyclanol (II) with lithium aluminum hydride.
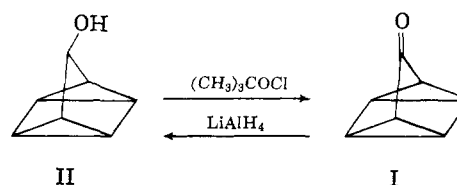
This highly strained ketone (I) is of interest because of its relation to the 7-quadricyclic carbonium ion[1] and because it is potentially the key intermediate in the synthesis of other 7-quadricyclic and 7-norbornadienyl derivatives, important to the understanding of bonding in these strained systems. The photochemistry of I is also potentially of considerable interest.

The stability of the 7-quadricyclic carbonium ion[1] would make it seem likely that the ionic structure Ia would contribute appreciably to the resonance hybrid. That this is the case is reflected in the apparently

large dipole moment of quadricyclanone (I). For example, the retention time of I is greater than that of the alcohol (II) on polar g.p.c. columns and the boiling point of I is also slightly higher than that of II. Although quadricyclanone (I) did not appear to be particularly deliquescent as reported for nortricyclanone,[2] it is quite water-soluble. Water solutions of I were found to be very weakly basic. Presumably water solubility could also be explained by hydration of I to a gem-diol, since formation of such a diol would be expected to result in considerable relief of the strain imposed by the trigonal carbonyl structure. We have examined the ultraviolet and n.m.r. spectra of I in water, however, and can find no positive evidence for the existence or absence of a gem-diol. The ultraviolet spectrum of I in water exhibited end absorption and a maximum at 293 mμ (ϵ 84). In ethanol the maximum was observed at 296 mμ (ϵ 66) and in cyclohexane at 297 mμ (ϵ 40). Obviously, the carbonyl is not completely hydrated to a diol.

The 60 Mc. n.m.r. spectrum of I in 97% deuterium oxide (0.4 M) consisted of a four hydrogen doublet 143 c.p.s. upfield from the water signal, which we have assigned to the β-hydrogens, and a two hydrogen triplet, 216 c.p.s. upfield from the water signal, assigned to the α-hydrogens. Some fine structure was visible in both multiplets. In carbon tetrachloride the

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(2) J. P. Schaefer, *ibid.*, **82**, 4091 (1960).

spectrum was unchanged, with the doublet appearing at τ 7.79 and the triplet at τ 8.98. In both solvents the coupling constant was 4.3 c.p.s. However, addition of deuteriotrifluoroacetic acid to the deuterium oxide solution reduced J to 3.9 c.p.s. without otherwise affecting the spectrum.

As expected, the infrared spectrum of quadricyclanone (I) in carbon tetrachloride indicated only cyclopropane-type hydrogens[3] with a single maximum at 3065 cm.$^{-1}$ in the C–H stretch region. The carbonyl stretching frequency was exceptionally low, occurring at 1746 cm.$^{-1}$ (5.73 μ). By comparison, the maxima of nortricyclanone,[2] 7-norbornone,[4] and 7-norbornenone[4,5] are reported at 1753 cm.$^{-1}$ (5.70 μ), 1780 cm.$^{-1}$ (5.62 μ), 1745 cm.$^{-1}$ (5.73 μ), and 1780 cm.$^{-1}$ (5.62 μ), respectively. Other significant maxima of I were observed at 1230, 996, 933, 898, and 846 cm.$^{-1}$.

Oxidation of 10 g. of 7-quadricyclanol (II)[1a] with 11 g. of t-butyl hypochlorite[6] in 9 g. of pyridine and 25 ml. of carbon tetrachloride according to the general procedure of Grob and Schmid[7] yielded 4.7 g. of crude product after short path distillation, b.p. 40° (2 mm.)–85° (0.5 mm.) Redistillation yielded 1.7 g., b.p. 50–55° (2 mm.), of still impure product containing 85% quadricyclanone (I) (14% yield) by g.p.c. analysis. The major impurity was unreacted quadricyclanol (II), b.p. 50–52° (2 mm.). The ketone (I) was purified by g.p.c. or by crystallization from pentane, m.p. 45–47°(cor.). *Anal.* Found for C_7H_6O: C, 78.64; H, 5.72. The melting point of I was unchanged after heating to 50° and resolidification in a partially evacuated capillary tube. On continued slow heating, the colorless liquid began to yellow at 140°. At 170° the dark red liquid began to bubble and at 200° only a dark tar remained. I reacted rapidly to form a 2,4-dinitrophenylhydrazone, m.p. 156–159° dec..

Acknowledgment.—We thank Mr. E. W. Anderson for the n.m.r. spectra and Mr. J. P. Luongo for determination of some of the infrared and ultraviolet spectra.

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An Active Center Histidine Peptide of α-Chymotrypsin

Sir:

Through the work of Balls and Jansen,[1] Oosterbaan, *et al.*,[2] and others,[3] it has been established that a unique serine residue of α-chymotrypsin is the ultimate site of acylation and phosphorylation with several quasi-substrates and inhibitors. Peptides with substituted serine residues have been isolated and their structures have been determined. This work gives strong evidence for the participation of a serine hydroxylic group in the catalytic mechanism of this enzyme. A histidine residue was also thought to have an important function in the hydrolytic mechanism, but could not be identified until the recent development[4]

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(3) N. K. Schaffer, S. C. Nay, and W. H. Summerson, *J. Biol. Chem.*, **202**, 67 (1953).

in this laboratory of a new, specific, active center reagent for chymotrypsin, TPCK, L-1-tosylamido-2-phenylethyl chloromethyl ketone, which has now been isolated as a peptide derivative from the inhibited enzyme.

TPCK, a chloromethyl ketone derived from L-phenylalanine, inactivates chymotrypsin by a stoichiometric alkylation judged to be at histidine from the observed loss of one residue of this amino acid on acid hydrolysis.[4] The two histidine residues present in α-chymotrypsin are both in the B-chain; consequently, to locate the inhibitor, degradative studies were carried out on the B-chain isolated from chymotrypsin, inactivated by TPCK-C^{14}. Reductive cleavage of the disulfide bridges was accomplished by means of sodium sulfite and Cu^{+2} in 8 M urea,[5] and the S-sulfo derivatives then were separated on a DEAE-cellulose column according to the procedure of Desnuelle and co-workers.[6] The amino acid composition of the modified B-chain revealed the expected loss of one histidine residue.

The modified B-chain was digested with pepsin at 37° for 12 hr.; the resulting peptide mixture was prepurified on a column of Sephadex G-50 with 0.2 N acetic acid as eluent. Only one radioactive peak emerged from the column, and further fractionation was carried out on Dowex 50-X2 using volatile pyridine acetate buffers. Final purification was achieved on a column of DEAE-Sephadex. A pure radioactive peptide was obtained which had the amino acid composition shown in Table I which was determined by amino acid analysis according to the method of Spackman, *et al.*[7]

TABLE I

AMINO ACID COMPOSITION OF ACTIVE CENTER PEPTIDE DERIVED FROM α-CHYMOTRYPSIN-TPCK-C^{14}

Residue	μmoles	Number of residues	Keil, *et al.*[8] peptide no. 17
Asp	0.100	1.00	1.00
Thr	0.186	1.86	1.83
Ser	0.106	1.06	0.91
Gly	0.112	1.12	1.10
Ala	0.195	1.95	1.94
0.5Cys	0.091	0.91	0.94
Val	0.105	1.05	1.00
His	0	0	0.98
Inhibitor C^{14}	0.105^a		

^{a} Based on specific activity of TPCK-C^{14}.

Since the chemistry of the alkylation of histidine with TPCK is still unknown, no positive identification of a histidine derivative could be made. The radioactivity of this peptide which was introduced by means of TPCK-C^{14}, and the consistency of our finding that the modified histidine residue cannot be identified using the standard procedure for amino acid analysis, leave, however, no doubt about the significance of our results. As is obvious from Table I, additional strong support comes from the fact that the analysis of the isolated decapeptide is in excellent agreement with the composition of a histidine peptide as reported by Keil, *et al.*[8]

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