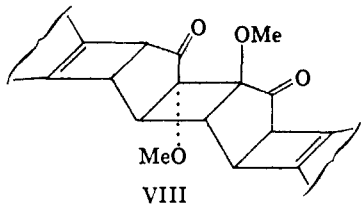

VIII

shift comes from examination of the resonance positions of the methoxyl protons in diol IVa (normal, 6.75 τ), ketoalcohol Va (normal 6.81 and shifted 6.90τ) and ketoacetate Vb (normal 6.75 and shifted 6.88τ). *The duality of the methoxyl resonance in Va and Vb offers unequivocal evidence of the dimeric nature of these compounds.* The N–H resonance in the diol IVa is strongly shifted to low field (1.95 τ) from the N–H resonance in II (3.28 τ). This shift is shown by all derivatives of II which possess an hydroxyl group and is the result of hydrogen bonding between the acetamido nitrogen and the nearest hydroxyl group. This is possible only if these groups are *cis*- thus defining the stereochemistry of IVa,b,c and Va,b. The duality of the N–H resonance in the monoacetate (1.76, 3.37 τ), the ketoalcohol (1.95, 3.60 τ) and the ketoacetate (3.15, 3.86 τ) emphasizes again the dimeric nature of these compounds.

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RECEIVED AUGUST 2, 1961

CONFIGURATIONAL ANALYSIS OF 4-FORMYL-1-METHYLPYRIDINIUM IODIDE OXIMES AND ITS RELATIONSHIP TO A MOLECULAR COMPLEMENTARITY THEORY ON THE REACTIVATION OF INHIBITED ACETYLCHOLINESTERASE

Sir:

Wilson[1,2] has offered the hypothesis that chemotherapeutic activity of 2-formyl-1-methylpyridinium iodide oxime in the treatment of "nerve gas" poisoning depends both on its ability to associate with inhibited enzyme at the site of phosphorylation and a proper orientation of the reactive oximino function for enzyme reactivation by nucleophilic displacement of the phosphate grouping. The *anti* configuration in the 2(and 4)-formyl-1-methylpyridinium oximes satisfied geometrical dispositions defined for the displacement reaction[2]; support for the contribution of geometric conformation regarding the reactivation rates of inhibited acetylcholinesterase was obtained from observations of enhanced activity of the "oximes" of the "anti" configuration.[2] Only 2-formyl-1-methylpyridinium iodide oxime was claimed sufficiently stable in the *"syn"* series for study and was not found active in reactivating inhibited acetylcholinesterase.[2] Subsequently, it was discovered that the unstable "*syn*" series compounds were carbinolamines, not oximes.[3]

Recent studies in these Laboratories have established that both geometrical isomers of isonicotinaldehyde oxime may be isolated.[4] The *syn* isomer

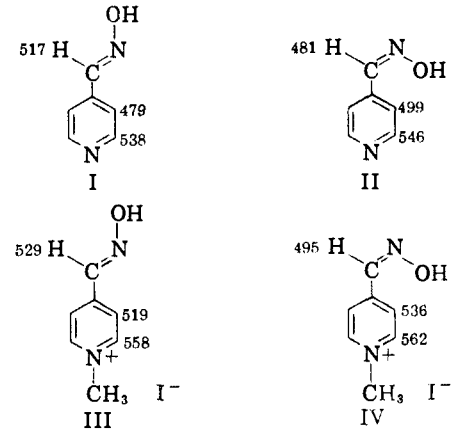

Fig. 1.—Nuclear magnetic resonance peaks (c.p.s.) of isonicotinaldehyde oximes and 4-formyl-1-methylpyridinium iodide oximes from spectra obtained by Varian Associates in deuterium oxide at 60 Mc. The ring proton resonances refer to doublets. Tetramethylsilane was used as internal reference at 0 with respect to observed resonance.

of isonicotinaldehyde oxime, I, m.p. 132–133°, was reported previously.[5] The other geometrical isomer, II, m.p. 165–167° (*Anal.* Found for $C_6H_6N_2O$: C, 58.8; H, 4.9; O, 13.3) was isolated in yields of less than 5% from isonicotinaldehyde and hydroxylamine in basic aqueous media at 10–15° by fractional crystallization from the *syn* isomer. This procedure was not satisfactory because of inconsistent reproducibility, but a better method was not found. Alkylation of I and II with methyl iodide yielded isomeric 4-formyl-1-methylpyridinium iodide oximes, III (m.p. 182–183°; reported[5] 181–183°, *pKa* 8.6) and IV, m.p. 169–172° (*Anal.* Found for $C_7H_9IN_2O$: C, 32.3; H, 3.3; O, 6.3; neut. equiv., 246; p*K*a 9.0), respectively.

On comparing the nuclear magnetic resonance spectra of I and II it was noted that the signal from the hydrogen on the oximino carbon was shifted chemically to lower field in the spectrum of I. This suggests by analogy with propionaldoxime,[6] that the hydrogen is *syn* to the oxime oxygen (Fig. 1). Additional strength for this assignment is found in the signals from the ring protons *ortho* to the oximino function which are chemically shifted further

(1) I. B. Wilson and S. Ginsburg, *Biochim. et Biophys. Acta*, **18**, 168 (1955).

(2) I. B. Wilson, *Federation Proc.*, **18**, 752 (1959).

(3) E. J. Poziomek, D. N. Kramer, B. W. Fromm and W. A. Mosher, *J. Org. Chem.*, **26**, 423 (1961).

(4) E. J. Poziomek, D. N. Kramer and W. A. Mosher, Abstr. 138th Meeting, Am. Chem. Soc., 1960.

(5) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).

(6) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958). Cited by J. A. Pople, W. G. Schreiner and H. J. Berstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 374. To check Phillips' assignment[6a] of the two —CH=NOH multiplets arising from *syn-anti* isomerism, Lustig[6b] examined the spectra of the two *p*-chlorobenzaldoximes in dimethyl sulfoxide solution. The —CH=NOH resonance of the *syn* oxime appeared at lower field and Phillips' assignment[6a] is substantiated. The structures of both isomers of *p*-chlorobenzaldoxime had been determined previously through X-ray diffraction studies.[6c] (b) E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961). (c) B. Jerslev, *Nature*, **166**, 741 (1950); **180**, 1410 (1958).

downfield in the spectrum of II; this would be expected from the closer positions of oxygen in this structure compared to that of I as shown by inspection of molecular models. The same interpretation is used in the spectra of III and IV and the results are consistent with this type of reasoning.

The rate of reactivation of Sarin inhibited eel acetylcholinesterase at pH 7.4, 25°, in the presence of 7.2×10^{-3} *M* acetylcholine by *syn*-4-formyl-1-methylpyridinium iodide oxime, III, was reported previously[7] as 140 $M.^{-1}$ $min.^{-1}$ while that of the *anti* isomer, IV, was 56 $M.^{-1}$ $min.^{-1}$. These results do not agree with the molecular complementarity theory advanced by Wilson which predicted that the *anti* isomer would be the more active reactivator.

(7) E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958).

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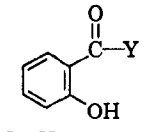
RECEIVED JULY 10, 1961

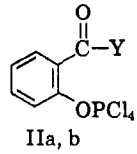
AN UNUSUAL HETEROCYCLIC SYSTEM INVOLVING CHARGE SEPARATION AND HEXACOVALENT PHOSPHORUS

Sir:

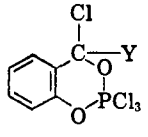
In a previous study[1] of the product from the reaction of phenyl salicylate (Ia) and phosphorus pentachloride, the absence of an infrared carbonyl stretching band served to eliminate structure IIa originally proposed by Michaelis and Kerkhof.[2] Structure IIIa was preferred over IVa on the basis of the available evidence. Since structure IIIa can be considered to be formed by the covalent sharing



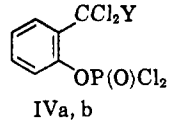
Ia, Y = C_6H_5O–
Ib, Y = C_6H_5–



IIa, b



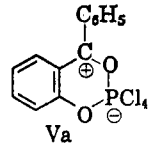
IIIa, b



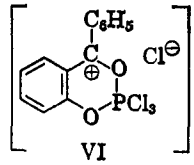
IVa, b

by phosphorus and oxygen of the π electron pair originally from the ester carbonyl group, it seemed that a more easily polarizable carbonyl such as that of a ketone would undergo a similar ring closure. Indeed, the infrared spectrum of the compound obtained from the reaction of *o*-hydroxybenzophenone (Ib) (practically quantitative yield) also showed no trace of a carbonyl stretching band. The product, which was very soluble in most common organic solvents, was recrystallized as colorless rods, m.p. 65.4–66.2° from cyclohexane. *Anal.*[3] Calcd. for $C_{13}H_9Cl_4PO_2$: C, 42.20; H, 2.45; Cl, 38.33; mol. wt., 370.0. Found: C, 42.08; H, 2.62; Cl, 38.21; mol. wt.,[4] 372.8. The compound was remarkably resistant to hydrolysis in contrast to the extreme sensitivity to moisture of the 1:1 products of a variety of phenols and phosphorus pentachloride.[5] For example, when a solid[5a] sample of the compound was shaken for several minutes with water, the filtrate gave no precipitate with silver nitrate. The compound was completely hydrolyzed, however, back to *o*-hydroxybenzophenone (81% yield) by refluxing with aqueous sodium hydroxide.

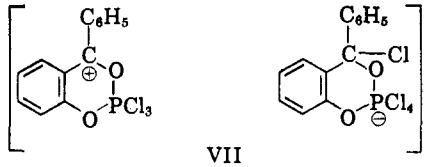
The dipole moment of the compound was surprisingly high (9.17 D. at 30° in benzene)[6]—much higher than that estimated on the basis of IIIb or IVb. A structure in full accord with the high dipole moment and other experimental data is V which incorporates a novel type of intracyclic charge separation. The accurate molecular weight determination eliminates a simple ionization such as VI as an explanation. The conductance of a benzene solution was too low to be measured. Furthermore, appreciable ionization would not be expected in benzene, a non-ionizing solvent. In acetonitrile, a more favorable solvent for ionization, the conductance was of a low order of magnitude. For example, the equivalent conductivity of a 0.04913 *M* solution was 0.05374 ohm^{-1} $cm.^2$. This can be compared with a value of 30.0 ohm^{-1} $cm.^2$ for a 0.0495 *M* solution of phosphorus pentachloride in acetonitrile[7] and 73.8 ohm^{-1} $cm.^2$ for a 0.0570 *M* solution of triphenyl phosphite dichloride in acetonitrile.[8] The low conductivity excludes appreciable amounts of an ionic dimer (VII) type of structure which would not be excluded by the molecular weight determination.



Va



VI



VII

The ultraviolet spectrum of the compound (cyclohexane) shows the absence of the low intensity long wave length band at 336 mu present in the spectrum

(1) A. G. Pinkus, P. G. Waldrep and P.-H. Ko, Abstracts, 132nd ACS Meeting, Chicago, Illinois, Sept. 7–12, 1958, p. 48-P.

(2) A. Michaelis and W. Kerkhof, *Ber.*, **31**, 2172 (1898).

(3) Carbon and hydrogen analyses by Clark Microanalytical Laboratory, Urbana, Illinois.

(4) Cryoscopic in benzene.

(5) R. Anschütz and W. D. Emery, *Ann.*, **239**, 301 (1887); A. G. Pinkus and P. G. Waldrep, *J. Org. Chem.*, **24**, 1012 (1959).

(5a) NOTE ADDED IN PROOF.—Solutions of the compound, however, hydrolyze at a faster rate; thus, all manipulations of solutions of the compound were carried out in a dry-box.

(6) A check determination on a known compound having a high dipole moment was made. The value obtained for N-benzylsydnone, 6.36 D., at 30° in benzene, checks closely with the value 6.27 D. at 25° in benzene reported by R. A. W. Hill and L. E. Sutton, *J. Chem. Soc.*, 746 (1949).

(7) D. S. Payne, *ibid.*, 1052 (1953).

(8) G. S. Harris and D. S. Payne, *ibid.*, 3038 (1956).