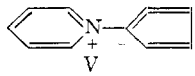
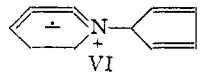
Lloyd and Sneezum have recently described the interesting compound pyridinium cyclopentadienylide (V),[35] a molecule which appears to behave as an "internal" charge-transfer complex. Salt-like character is shown by the lack of a melting point (did not melt under 350°) and low solubility in non-polar solvents. Addition of the anion to the pyridinium ring to give a highly trained tricyclic compound, which would be electrically neutral, is rather improbable thermodynamically. Yet, the solutions are intensely colored, varying from colorless in acidic aqueous solution (proton addition to give the colorless 1-alkylpyridinium ion) through yellow in alkaline aqueous solution, orange in alcohol, red in acetone and chloroform, reddish-



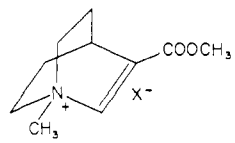
V



VI

purple in benzene and ether and bluish-purple in petroleum ether. The variation in color with solvent dielectric constant is precisely what would be predicted for a charge-transfer complex in which the ionic ground state was becoming progressively destabilized through loss of solvation energy with respect to an "uncharged" excited state, VI, thus shifting light absorption to longer and longer wave lengths. A similar, smaller, but apparently analogous shift has been found for 1-methylpyridinium iodide when the solvent is changed from water to ethanol.[26]

It has been shown that the bicyclic quaternary salts, VII (X = Cl^-, Br^-, I^-), do not obey Beer's



VII

law in aqueous solution,[36] and a charge-transfer complex is probably present.

The colors of tropylium salts[37] can also be explained on the basis of charge-transfer complex formation. Doering and Knox[38] have reported that 7-methoxy-1,3,5-cycloheptatriene (tropyl methyl ether) is a colorless liquid, and measurement of the spectrum of 7-hydroxy-1,3,5-cycloheptatriene (tropyl alcohol; tropylium ion at high *p*H in water) gave a curve with a clear maximum, λ_{max} 2510 Å., log ϵ 4.00. Tropylium ion possessed an absorption maximum at 2750 Å., log ϵ 3.64. Although Doering and Knox say that ". . . the yellow color of the cation is due to a long tailing . . ." (in the absorption band), this does not explain the colors found for the solid tropylium halides, chloride, pale yellow,[38] white[37]; bromide, yellow[37,38]; iodide, *black*.[37] While the color of solid salts is hardly a reliable index of events on the molecular level, it seems significant that such a range of colors exists between the tropylium ion on the one hand and the covalently bonded and colorless tropyl methyl ether on the other. If the charge-transfer complex is indeed the logical intermediate in nucleophilic additions, then it ought to be present in certain tropylium ion–anion combinations. The series of colors observed for the halides is consistent with this possibility, but a definitive proof must await an investigation of the type carried out in this and the previous paper.[2]

Acknowledgment.—The authors would like to express their appreciation to Mr. John C. Burbach for obtaining some of the spectral data and for other valuable technical assistance.

(35) D. Lloyd and J. S. Sneezum, *Chemistry and Industry*, 1221 (1955).

(36) C. A. Grob and E. Renk, unpublished results in private communication from Prof. C. A. Grob, Organisch-chemische Anstalt der Universität, Basel, Switzerland.

(37) R. Pettit, paper presented at the XIVth International Congress of Pure and Applied Chemistry, Zürich, Switzerland, July 26, 1955.

(38) W. v. E. Doering and L. H. Knox, THIS JOURNAL, **76**, 3203 (1954).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, LEHIGH UNIVERSITY]

Additions to Pyridinium Rings. III. Chemical and Biochemical Implications of Charge-Transfer Complex Intermediates

BY EDWARD M. KOSOWER

RECEIVED NOVEMBER 29, 1955

Consideration of the occurrence of charge-transfer complexes formed from 1-methylpyridinium ions and electron donors together with data from the literature suggest the following conclusion regarding addition to pyridinium rings. Donors which form complexes substitute at the 4-position and those which do not, or do so only poorly, substitute at the 2-position. It is also proposed that the previously observed complexes formed from diphosphopyridine nucleotide (DPN) and enzymes, and those from DPNH and enzymes are charge-transfer complexes. A consequence of the importance of donor ability in determining position of addition leads to a revision of the schematic mechanism for the reaction of ethanol and DPN.

A spectral study of aqueous solutions of 1-methylpyridinium iodide showed that a new species was present.[1] Similar studies using substituted 1-methylpyridinium iodides suggested that the new species was a charge-transfer complex[2] and that these complexes may be intermediates in the addition of nucleophiles to the pyridinium ring.

A tabulation of the results of addition to pyridinium rings, made in Table I, reveals that nucleophiles which form charge-transfer complexes easily, or which might be expected to do so (*cf.* the following Discussion), add at the 4-position, while

(1) E. M. Kosower, THIS JOURNAL, **77**, 3883 (1955).

(2) E. M. Kosower and P. E. Klinedinst, Jr., *ibid.*, **78**, 3493 (1956).

TABLE I

PRODUCTS OF ADDITION TO PYRIDINIUM RINGS

Addend[a]	R[b]	R'[c]	2-addn.[v]	4-addn.	Proo	Ref
$C_6H_5NH_2$	CN—	[d]	x		RO[e]	6
$C_6H_5NH_2$	2,4-$(NO_2)_2C_6H_3$—	[f]	x		RO[g]	7
OH^-	2,4-$(NO_2)_2C_6H_3$—	[h]	x		RO[e]	7
OH^-	CH_3—	[f]	x		oxid.[i]	8
$OC_2H_5^-$	2,4-$(NO_2)_2C_6H_3$—	[h]	x		RO[j]	9
$C_6H_5COCH_2^-$	C_6H_5CO—	[h]	x[k]	x	isol., syn.[l]	10
$(C_6H_9O)^-$[m]	C_6H_5CO—	[h]		x	oxid. to INA[n]	10
$(CH_3)_2NC_6H_5$	C_6H_5CO—	[h]		x	isol.[o]	11
CN^-	APPR[p]	[q]		x	Deut. exch.	12
$HOCH_2COCHOH^-$	APPR	[q]		x	Spectra[r]	13
$CH_3COCH_2^-$	APPR	[q]		x	Spectra	14
HSO_3^-	APPR	[q]		x	Spectra	15
$S_2O_4^=$	APPR	[q]		x	Formn. of DPNH[s]	16
$S_2O_4^=$	CH_3^-	[q]		x	Oxidn. to pyridones[t]	17
$S_2O_4^=$	$C_6H_5CH_2$—	[q]		x	Deut. transf.[u]	18

[a] To simplify the presentation of the data, enolate ions have been listed, although, in fact, the enols may have been the reactive species. Where a number of similar cases may be known, only one is listed unless the reaction is of particular importance. This restriction was applied especially to carbonyl compounds and to aromatic amines. [b] The 1-substituent on the pyridinium ring. [c] The ring substituent, if any, on the pyridinium ring (other than 1-). [d] None or 2-methyl. [e] A ring-opened product was isolated, containing the five-carbon chain derived from the pyridinium ring. [f] None or 3-carbamyl.[19] [g] Dianilide of glutacondialdehyde. [h] None. [i] Oxidation is a valid measure of 2-addition, *if* the pseudobase *is* the intermediate. [j] Cyanine dyes are formed by the reaction of various substances with the ring-opened product. [k] Some 2-addition is suggested by the authors on the basis of a speculative mechanism for the formation of the O-acyl derivative of acetophenone. It is clearly of lesser quantitative significance than 4-addition. [l] A product was isolated which was converted into a synthesizable derivative, 4-phenacylpyridine. [m] Enolate ion of cyclohexanone. [n] Isonicotinic acid. [o] 4-(*p*-Dimethylaminophenyl)-pyridine was actually isolated and presumed to result from the decomposition of the expected product, 1-benzoyl-4-(*p*-dimethylaminophenyl-)-1,4-dihydropyridine. [p] The non-nicotinamide moiety of diphosphopyridine nucleotide (DPN); adenosinediphosphate-ribosyl-. [q] 3-Carbamyl. [r] The spectrum of the product closely resembled that of DPNH, which has been shown to carry its "extra" hydrogen on the 4-position. The actual difference between the ultraviolet absorption spectra of 1,4-dihydro- and 1,2-dihydropyridine derivatives has never been ascertained. [s] Although the nature of the addition product and the mode of its decomposition are still unknown, we shall presume, along with Colowick and Yarmolinsky,[16] that it is a 4-adduct. [t] The 1-methylpyridinium compound was reduced with hyposulfite ion in deuterium oxide, followed by reoxidation to a deuterated 1-methylpyridinium ion and *then*, by oxidation to pyridones. [u] The dihydro compound derived from 4-deuteronicotinamide transferred deuterium to malachite green; those derived from the 2- and 6-isomers did not, in the same reaction, transfer deuterium. [v] x signifies addition at a particular position.

those nucleophiles which probably do not form complexes, or do so only to a very limited extent, add at the 2-position. Since no information is available on complex formation for the listed nucleophiles, except insofar as their relation to iodide ion may be known, it is necessary to consider certain indirect arguments with respect to complex formation.

Criteria for Complex Formation.—In charge-transfer complexes, donors contribute electronic charge and acceptors receive it. Therefore, the ionization potential of the donor and the electron affinity of the acceptor might be expected to reflect their respective abilities.[3] The actual energy of interaction of donor and acceptor is modified by coulombic forces, changes in solvation with complex formation, steric factors, etc., and valid predictions of the extent of complex formation are thus difficult. However, some uncertainty is avoided if all considerations are referred empirically to the case of the 1-methylpyridinium–iodide ion interaction in which a charge-transfer complex *is* found. Donors which release electronic charge about as well as iodide ion would form a complex. Substituents on the pyridinium ring which were more effective at electron withdrawal than the methyl group would be expected to increase the electron affinity of the pyridinium ring. All of the substituents mentioned in Table I are in this category with the exception of methyl itself.

Donor properties are more difficult to assess, but two indices are available which cover almost all of the examples used in Table I. The electrode potential for the reaction $2X^- \rightleftarrows X_2 + 2e^-$ may be used as a measure of the ability to donate charge,[4] with a recalculated value for the cyanide ion based upon the results of Hawthorne, *et al.*[5] Values for the relevant potentials are listed in Table II.

(3) R. S. Mulliken, THIS JOURNAL, **74**, 811 (1952).
(4) J. O. Edwards, *ibid.*, **76**, 1540 (1954).
(5) M. F. Hawthorne, G. S. Hammond and B. M. Graybill, *ibid.*, **77**, 486 (1955).
(6) W. König, *J. prakt. Chem.*, **69**, 105 (1904).
(7) Th. Zincke, *Ann.*, **330**, 361 (1904).
(8) M. E. Pullman and S. P. Colowick, *J. Biol. Chem.*, **206**, 121 (1954).
(9) N. I. Fisher and F. M. Hamer, *J. Chem. Soc.*, 189 (1933).
(10) W. von E. Doering and W. E. McEwen, THIS JOURNAL, **73**, 2104 (1951).
(11) W. E. McEwen, R. H. Terss and I. W. Elliott, *ibid.*, **74**, 3605 (1952).
(12) Private communication from Dr. A. San Pietro, McCollum–Pratt Institute, Johns Hopkins University, Baltimore, Md.
(13) R. M. Burton and N. O. Kaplan, *J. Biol. Chem.*, **206**, 283 (1954).
(14) S. P. Colowick, N. O. Kaplan and M. M. Ciotti, *ibid.*, **191**, 447 (1951).
(15) O. Meyerhof, P. Ohlmeyer and W. Mohle, *Biochem. Z.*, **297**, 113 (1938).
(16) S. P. Colowick and M. Yarmolinsky in "Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, Md., 1954, p. 353.
(17) G. W. Rafter and S. P. Colowick, *J. Biol. Chem.*, **209**, 773 (1954).
(18) D. Mauzerall and F. H. Westheimer, THIS JOURNAL, **77**, 2261 (1955).
(19) H. Lettré, W. Haede and E. Ruhbaum, *Ann.*, **579**, 123 (1953).

TABLE II

ELECTRODE POTENTIALS

Ion	E°
$SO_3^{=a}$	−0.03
I^-	−0.536
CN^-	−0.56[b]
SCN^-	−0.77
OH^-	−0.95

[a] Hyposulfite, $S_2O_4^=$, is unstable with respect to sulfite over the whole *p*H range, although much more so in alkaline solution. It would be expected that its electrode potential would be somewhat more positive than that listed for $SO_3^=$.[20] [b] Estimated from the data given by Hawthorne, *et al.*

The second index of donor ability is much more qualitative. The ionization process generally leads to a free radical, *e.g.*, $C_6H_5COCH_2^- \rightarrow C_6H_5CO\text{-}CH_2$. One may estimate the ionization potential of the enolate ion of cyclohexanone as 67.5 kcal./mole, ignoring solvation energies.[21] This may be compared with the value of 76 kcal./mole for iodide ion.[26] Other ketones should not differ appreciably unless they are much more acidic than cyclohexanone, thus stabilizing the enolate ion relative to the free radical formed by dissociating the carbon–hydrogen bond. Thus, Burton and Kaplan[13] found that 1,3-pentanedione was unreactive toward DPN under conditions where dihydroxyacetone reacted rapidly.

The striking divergence in the behaviors of aniline and dimethylaniline is not explicable at the moment. It is known that substitution of methyl groups for hydrogen on the nitrogen atom of amines leads to a reduction of the ionization potential.[27] Zincke has reported that tertiary amines do not react with 1-(2,4-dinitrophenyl)-pyridinium chloride, whereas primary and secondary amines readily do so.[7]

The foregoing considerations allow us some confidence in the original statement that, in general, 4-substitution occurs with reactants that might reasonably be expected to form charge-transfer complexes. A substantial body of quantitative information will be required before subsidiary factors are brought to light and examined. Doering and McEwen[10] proposed that acylpyridinium ions reacted at the 4-position while alkylpyridinium ions reacted at the 2-position, but the demonstration of 4-addition for 3-carbamyl-1-methylpyridinium iodide by Rafter and Colowick[17] does not accord with this suggestion.

Charge-transfer Complexes in Biochemistry.—When the results of biochemical experiments require that interactions between two of the species present in the system be postulated, three general classes of interactions are usually considered, electrostatic attraction or repulsion,[28] compound formation[29] and unspecified complex formation.[30] Mulliken suggested that charge-transfer complexes "may afford new possibilities for understanding intermolecular interactions in biological systems."[3] Classification of unspecified complexes as charge-transfer types would be an advance because the charge-transfer types will have recognizable spectral and chemical behavior.

The importance of the pyridine nucleotides in metabolic processes[31] justifies the most detailed kind of inquiry into their properties and mode of action. The discovery that pyridinium ions form charge-transfer complexes[2] led to a re-examination of the sparse data on the pyridine nucleotides to determine whether the presence of this type of complex was indicated. Westheimer and Vennesland[32] have demonstrated that hydrogen is transferred directly from the substrate to the coenzyme, DPN, thus accomplishing a brilliant forward step in the elucidation of the mechanism of enzyme reactions.[33] Colowick[34] utilized this result in proving that the hydrogen was transferred to the 4-position of the pyridinium ring. The reaction is stereospecific with respect to the pyridinium ring[32] and with respect to the substrate in the case of ethanol.[35] The present set of comments, together with the theory concerning the position of addition to pyridinium rings proposed in the first part of this paper, should aid in the understanding of behavior of the pyridine nucleotides.

DPN–enzyme Complexes.—Chance[36] has summarized the spectroscopic evidence for these complexes. By measuring the differential absorption for an enzyme solution with and without DPN, Chance could demonstrate a rather flat maximum for a complex at about 3600 Å. with both yeast and mammalian glyceraldehyde-3-phosphate dehydrogenases. Racker and Krimsky[37] had obtained a similar result previously by splitting the

(20) W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1952, p. 77.

(21) If we write the equilibria, cyclohexanone ⇄ cyclohexanone enol ⇄ cyclohexanone enolate anion, we see that the ionization potential will be the difference in energy required to dissociate the H–C bond next to the carbonyl group and that required to convert the ketone to the enolate anion. The enol content of cyclohexanone has been measured[22] and corresponds to a K for the first equilibrium of 2×10^{-4}. The dissociation constant is assumed equal to that for phenol, 1×10^{-10}. The energy required to dissociate the H–C bond is estimated as 87 kcal./mole.[23] Thus, ignoring solvation energies, the ionization potential is 87 minus 19.5 or 67.5 kcal./mole.

(22) G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 669 (1947).

(23) Since acetonyl iodide dissociates more readily than ethyl iodide,[24] and, in fact, lies closer to benzyl iodide than ethyl iodide, we have selected an H–C dissociation energy about halfway between that for H-ethyl and H-benzyl.[25]

(24) E. W. R. Steacie, "Atomic and Free Radical Reactions," Reinhold Publ. Corp., New York, N. Y., 1946, p. 146.

(25) T. L. Cottrell, "The Strengths of Chemical Bonds," Butterworths Scientific Publications, London, 1954.

(26) Y. K. Syrkin and M. E. Dyatkina, "Structure of Molecules and the Chemical Bond," Interscience Publishers, New York, N. Y., 1950.

(27) W. C. Price, *Chem. Revs.*, **41**, 257 (1947).

(28) *Cf.*, for example, I. B. Wilson, "Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, Md., 1954, pp. 642–657.

(29) *E.g.*, peroxidase–hydrogen peroxide reaction intermediates, B. Chance, *Advances in Enzymology*, **12**, 153 (1951).

(30) H. B. Bull, "Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, Md., 1954, pp. 141–153.

(31) *Cf.* reviews by T. P. Singer and E. B. Kearney, *Advances in Enzymology*, **15**, 79 (1954) and E. Racker, *Physiol. Revs.*, **35**, 1 (1955).

(32) H. F. Fisher, E. E. Conn, B. Vennesland and F. H. Westheimer, *J. Biol. Chem.*, **202**, 687 (1953).

(33) Direct transfer disposes of, for example, the plausible theory of T. A. Geissman, *Quart. Rev. Biology*, **24**, 309 (1949).

(34) M. Pullman, A. San Pietro and S. P. Colowick, *J. Biol. Chem.*, **206**, 129 (1954).

(35) F. A. Loewus, F. H. Westheimer and B. Vennesland, THIS JOURNAL, **75**, 5018 (1953).

(36) B. Chance, "Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, Md., 1954, pp. 433–452.

(37) E. Racker and I. Krimsky, *J. Biol. Chem.*, **198**, 731 (1952).

complex with iodoacetic acid. Another, more intense absorption maximum at 2400 Å. was found by using hydrogen peroxide to split the complex.[36] In contrast, although yeast alcohol dehydrogenase binds DPN,[38] no complex formation could be detected spectroscopically.[36] Without knowledge about the charge-transfer complexes formed by 3-carbamyl-1-alkylpyridinium ions, it is not possible to assign definitely the 3600 Å. maximum to such a complex. This formulation is favored, though, by the broad, rather featureless quality of the absorption band, a recurrent characteristic of charge-transfer complexes.[39] The short wave length maximum at 2400 Å. could well be due to a displaced pyridinium ring absorption, as it has already been shown that the absorption maximum of the acceptor, iodine, in benzene–iodine complexes, is shifted to shorter wave lengths by complex formation.[3] The failure to detect complex formation spectroscopically may be due to (a) the use of concentrations that were too low to permit appreciable complex formation,[40] (b) a large contribution from electrostatic binding forces in particular cases[41] or (c) the less likely, but conceivable possibility that charge-transfer complex formation takes place with very little change in spectrum in certain instances.

DPNH–enzyme Complexes.—Chance[36] has listed the complexes known for reduced DPN and various enzymes. Lactic dehydrogenase gives a broad band with a maximum at 3300 Å., while horse liver alcohol dehydrogenase has a fairly well-defined band with a maximum at 3250 Å. It seems certain that these complexes are, in fact, charge-transfer complexes, partly on the basis that the new absorptions are reasonable in the light of such an interpretation and partly because any "chemical" binding (that is, formation of a bond by addition of an enzyme grouping to the DPNH molecule) would seriously decrease the length of the conjugated absorption system and thus prevent absorption at the wave lengths actually observed. It is not clear, however, whether DPNH should behave as a donor or as an acceptor; a DPNH donor might be able to bind carbonyl compounds before hydrogen transfer, and a donor activity is thus favored. Studies with model 1,4-dihydropyridine derivatives are planned to judge the extent and type of complex formation.

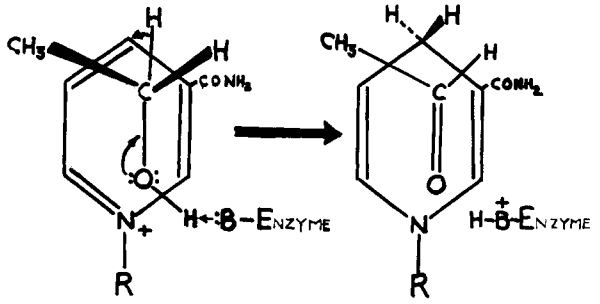
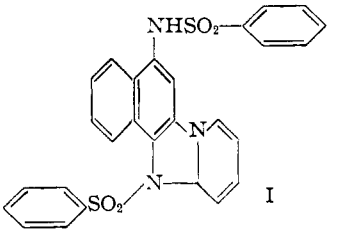


Fig. 1.—A schematic mechanism for the reaction of ethanol with DPN (diphosphopyridine nucleotide).

DPN–substrate "Complexes."—Burton and Kaplan[42] discovered that a high concentration of hydroxylamine reacts with DPN in the presence of hydroxide ions to give a product with ultraviolet absorption at 3150 and 2600 Å. The reaction is reversed on lowering the *p*H. Just as the absorption maximum for DPNH is shifted to shorter wave lengths on binding with enzyme, the absorption maximum for the DPN–NHOH product when bound by enzyme moves to shorter wave lengths. The enzyme–DPN–NHOH complex is formed at much lower hydroxylamine concentrations than the DPN–NHOH product itself.

On the basis of these observations, Burton and Kaplan advance two hypotheses, one, that the monoanion of hydroxylamine adds at the 4-position of the pyridinium ring and two, that the reaction of ethanol with DPN proceeds by ethoxide ion addition to the 4-position of the ring, followed by intramolecular transfer of hydrogen from the ethyl group to the pyridinium ring through a four-membered ring transition state.

According to the considerations stated in the early part of this paper, hydroxylamine anion and ethoxide ion should not complex readily with the pyridinium ring and would therefore add at the *2-position* of the ring. The stability of the hydroxylamine adduct in basic solution is not unexpected; Adams and Pomerantz[43] have isolated an unstable compound, I, from the reaction of pyridine and the N,N′-dibenzenesulfonyl derivative of 1,4-naphthoquinonediimide.



I

There is an additional objection to the proposed ethanol–DPN reaction mechanism, besides that of probable 2-addition for ethanol. The transfer of hydrogen is postulated as a 1,3-intramolecular hydrogen shift in an *uncharged* intermediate. No adequate analogy for this important step is known to the writer. Furthermore, the mechanism seems weak with regard to such details as possible interaction between DPNH and acetaldehyde and the very rigid stereochemical requirements which must be associated with the transition state in the presence of the enzyme.[32,35]

(38) S. F. Velick, "Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, Md., 1954, p. 494.

(39) L. E. Orgel, *Quart. Revs.*, **8**, 422 (1954).

(40) The dissociation constant for the yeast enzyme–DPN complex is 5–10 times greater than that of the mammalian glyceraldehyde-3-phosphate dehydrogenase. Ref. 38, p. 495.

(41) L. Astrachan has investigated the rates of reaction of bound DPN with various enzymes and has concluded that electrostatic binding through the pyrophosphate group is important. "Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, Md., 1954, p. 534.

(42) R. M. Burton and N. O. Kaplan, *J. Biol. Chem.*, **211**, 447 (1954).

(43) R. Adams and S. H. Pomerantz, THIS JOURNAL, **76**, 702 (1954).

A schematic mechanism for the ethanol–DPN reaction is presented in Fig. 1. It allows for electrostatic binding of the oxygen to the positively charged nitrogen of the pyridinium ring, for the stereospecificity of the reaction and for possible charge-transfer complex formation between DPNH and acetaldehyde.

Acknowledgment.—I would like to thank Dr. Robert West of this Department for helpful discussion.

BETHLEHEM, PA.

[CONTRIBUTION FROM THE JULIAN LABORATORIES, INC.]

Studies in the Indole Series. XV.[1] Dioxindole-3-propionic Acid

BY PERCY L. JULIAN, HELEN C. PRINTY AND EARL E. DAILEY

RECEIVED DECEMBER 30, 1955

Dioxindole is condensed with dihydropyran to yield the crystalline tetrahydropyranyl ether (VIII). Michael condensation of the latter with ethyl acrylate, followed by alkaline and then acid hydrolysis, gives dioxindole-3-propionic acid (XII), identical with the product secured several years ago by Kendall by oxidizing oxindole-3-propionic acid with iodine in sodium hydroxide solution.

As part of our long-pursued interest in providing 3-alkylated indole derivatives for use in the syntheses of substances related to natural products, our attention turned to the possibility of alkylating dioxindoles at the 3-position. The present paper describes the preparation of dioxindole-3-propionic acid.

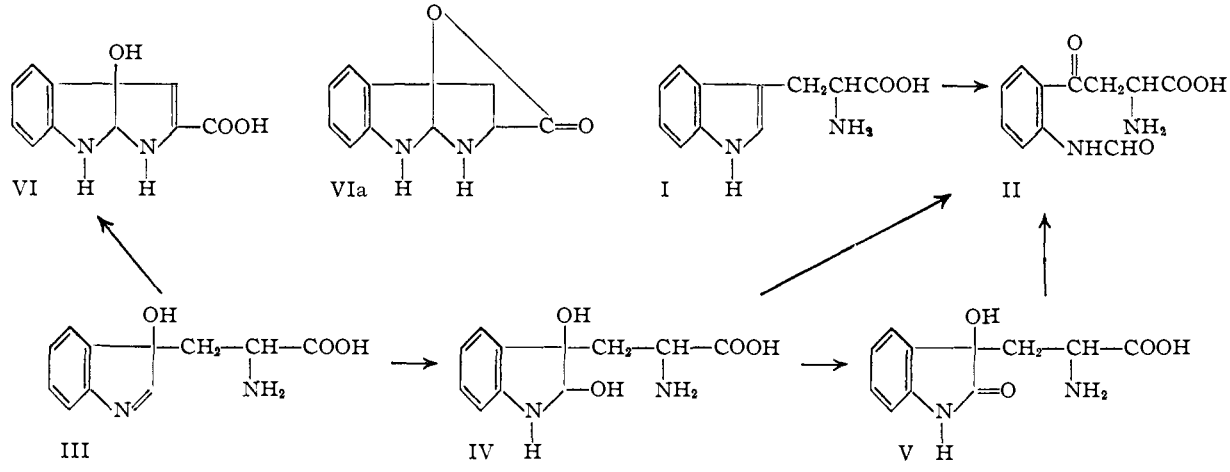
The impetus to this endeavor resided in the still existing necessity for demonstrating experimentally a plausible mechanism for the metabolic pathway by which oxidative rupture of the indole nucleus of tryptophan (I) produces N-formylkynurenine (II).

While Witkop[2] believes that "the actual intermediate" in this biological transformation is 3-hydroxyindolenine-3-alanine (III), he at the same time recognizes the almost practical impossibility of preparing such a substance because of the expected ease with which intramolecular ring closure of III to the eserine-like ring system (VI or VIa) would take place. He, therefore, suggests that III might undergo hydration to the glycol IV, which can either go to II *via* oxidative rupture, or might be converted into dioxindole-3-alanine (V). The latter may be considered an acyloin produced by internal condensation of N-formylkynurenine (II).

Of all these speculations it appears that the one which lends itself to probable immediate experimental verification is the route V → II, since the synthesis of V should be realized from a study of C_3-alkylation of dioxindoles. Although the literature records no such alkylations, it appeared that a synthesis of authentic dioxindole-3-propionic acid might well be the most appropriate starting point.

It should be expected that the electron induction of the C_3-hydroxyl group of dioxindole (VII) would so increase the acidity of the C_3-hydrogen atom that dioxindole might well alkylate as readily as or more readily than 3-alkyloxindoles.[3] Any alkali-induced condensations, however, must reckon with the possible enediol character of dioxindole. Also it must be recalled that in the Michael condensation, for example, indole gives with ethyl acrylate indole-1-propionic ester.

Actual attempts to condense dioxindole with ethyl acrylate in the presence of alkali alcoholates led to deeply colored mixtures and finally to intractable tars. It was obvious that suitable replacement of the hydrogen of the C_3-hydroxyl had to be provided. The tetrahydropyranyl ethers of dioxindoles were found to be the best derivatives



(1) For paper XIV in this series see THIS JOURNAL, **75**, 5305 (1953).

(2) A. Ek, H. Kissman, J. B. Patrick and B. Witkop, *Experientia*, **8**, 36 (1952).

(3) P. L. Julian, J. Pikl and D. Boggess, THIS JOURNAL, **56**, 1797 (1934); P. L. Julian and J. Pikl, *ibid.*, **57**, 539, 563, 755 (1935); E. C. Horning and M. W. Rutenberg, *ibid.*, **72**, 3534 (1950).