

Anal. Calcd. for $C_7H_{11}NO_2$: N, 9.92. Found: N, 10.02.

β -Ethylglutarimide.—This imide was prepared in a manner similar to that for the α -isomer starting with β -ethylglutaric acid, which was made by the procedure of Jeffery and Vogel.²⁵ It had a m. p. 88–89°. Sircar²⁶ gives m. p. 87°.

Absorption Spectra.—The ultraviolet spectra were determined in 95% ethanol solution using a Beckman Model DU spectrophotometer. The infrared spectra

(25) Jeffery and Vogel, *J. Chem. Soc.*, 446 (1939).

(26) Sircar, *ibid.*, 600 (1927).

were obtained on a Baird recording infrared spectrophotometer. Pertinent data are included with the spectrograms.

Summary

1. Actidione, a new antibiotic isolated from *Streptomyces griseus*, has been shown to have the structure I.

2. A number of reactions and transformations of Actidione have been carried out.

INDIANAPOLIS, INDIANA

RECEIVED JULY 10, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Kinetics of Pyrrole Substitutions. The Iodination Reaction¹

BY KENNETH W. DOAK² AND ALSOPH H. CORWIN

Wibaut³ first showed that the presence of a methyl group in the benzene ring greatly increases its reactivity toward nitration. Ingold and Shaw⁴ conclude that the rate of nitration by nitric acid in acetic anhydride is increased about 40–55-fold in each ortho and para position, while the reactivity in a meta position is increased threefold. McDuffie and Dougherty⁵ have observed that toluene is acetylated about thirteen times as rapidly as benzene. The explanation for this increased reactivity is given in the general electronic theory of organic reactions, developed to a large extent by Lapworth, Robinson and Ingold,⁶ which assumes that the attacking reagent seeks a pair of electrons from the aromatic nucleus. The methyl group facilitates the donation of an electron pair, by favoring polarization of the type $CH_3^+ \text{---} \text{C}_6\text{H}_5^-$ and thus lowering the energy of the activated intermediate.⁷

Kinetic investigations of substitution reactions are entirely lacking in pyrrole chemistry. A fundamental difference between the benzene and pyrrole systems exists, since the major resonance in benzene is between two normal valence forms while the resonance in pyrrole⁸ is mainly ionic, involving five principal structures.^{8b} The ionic structures should have fairly low energy, since no octets are broken and no double bonds are lost.

(1) Studies in the Pyrrole Series. XXII. Paper XXI, Corwin and Straughn, *THIS JOURNAL*, **70**, 2968 (1948). This work represents a portion of a doctoral dissertation by Kenneth W. Doak, The Johns Hopkins University, Baltimore, Md.

(2) The William R. Warner and Co., Inc., Fellow, The Johns Hopkins University. Present address: United States Rubber Company, Passaic, New Jersey.

(3) Wibaut, *Rec. trav. chim.*, **34**, 241 (1915).

(4) Ingold and Shaw, *J. Chem. Soc.*, 2918 (1927); 1959 (1931); 905, 918 (1938).

(5) McDuffie and Dougherty, *THIS JOURNAL*, **64**, 297 (1942).

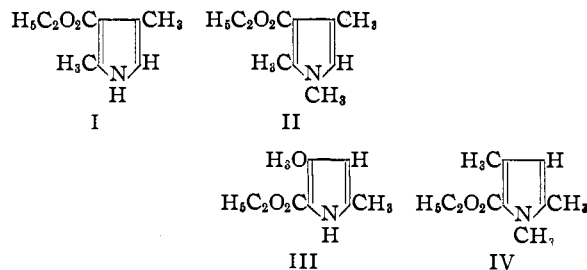
(6) Ingold, (a) *Rec. trav. chim.*, **48**, 797 (1929); (b) *J. Chem. Soc.*, 1120 (1933); (c) *Chem. Rev.*, **15**, 225 (1934); (d) Robinson, "Outline of Electronic Theory of Organic Reactions," Inst. of Chem. of Gr. Br. and Ireland, London (1932).

(7) Wheland, *THIS JOURNAL*, **64**, 900 (1942).

(8) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 137.

The large contribution of these structures to the normal state of the molecule makes the nitrogen positive, with the result that the N—H group is weakly acidic⁹ instead of basic, as would be expected for a secondary amine. Activated structures involving them probably have much lower energy than the activated structures in benzene; this accounts for the well-known fact that pyrrole is more reactive than benzene to electron-seeking reagents. For example, when pyrrole is treated with bromine, chlorine or iodine, in dilute solution, the mono-alpha derivative is formed first. If excess halogen is used, the tetrahalogenated pyrrole is formed^{10a} more readily than mono-halogenated benzenes.

In order to obtain kinetic data upon the substitution of pyrroles, the velocity of iodination of four pyrrole derivatives has been measured.



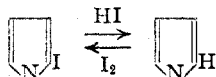
In the presence of potassium iodide in a buffered solution, the iodinations proceed almost to completion with velocities which can be measured accurately. Pyrroles which have substituents in all α - and β -positions except one were chosen in order to eliminate competing reactions. The N-methylated compounds were studied in order to determine whether or not the N-methyl group has an effect similar to that of a methyl group in the benzene nucleus. A comparison of pyrroles II and IV, in which steric effects should be quite

(9) Bamberger, *Ber.*, **26**, 1946 (1893); McEwen, *THIS JOURNAL*, **58**, 1124 (1936); Ingold and Goss, *J. Chem. Soc.*, 1268 (1938).

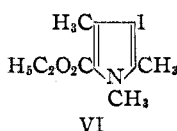
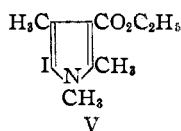
(10) Fischer, "Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft m. b. H., Leipzig, 1934, (a) p. 75, 83, 101; (b) p. 102.

similar, should give an estimate of the relative reactivities of an α - and β -position. These relative rates may be altered somewhat by the fact that the substituent methyl and carbethoxy groups are not quite equivalent in both pyrroles, due to the fact that one ring member is nitrogen. In each pyrrole, however, there are two methyl groups alpha to the reactive center, and a methyl and a carbethoxy group beta to it.

The reverse reaction, the reduction of an α - or β -iodopyrrole to an α - or β -free pyrrole, will occur



in a solution of hydriodic acid. Two experiments were carried out in order to obtain the approximate relative velocities of reduction of two iodo-pyrroles, V and VI.



Experimental

Method for Measurement of Velocities of Iodination.—These velocity measurements were carried out in aqueous dioxane (28% dioxane by weight) buffered by monosodium phosphate and disodium phosphate (0.035 *M* each) to a *pH* of 6.8–6.9. This was necessary to remove the hydriodic acid formed and drive the reaction to completion. The temperature was $26.5 \pm 0.1^\circ$. Solutions of the pyrroles (0.020–0.035 *M*) were made up by dissolving them in dioxane freshly distilled from sodium amalgam. The reactions were started by adding to 40 cc. of pyrrole solution 100 cc. of a aqueous iodine solution (0.0075–0.0120 *M*) containing 0.049 *M* phosphates and a large concentration of potassium iodide (0.560–1.200 *M*). The ionic strength was kept constant by the addition of sodium chloride. At intervals throughout the course of a reaction, 10.00-ml. samples of the reaction mixture were pipetted into 5.00 ml. excess standard sodium arsenite to destroy the iodine. This solution was buffered to a *pH* of 7.0 or slightly greater by addition of 1 ml. of monosodium phosphate (0.25 *M*) and 3 ml. of disodium phosphate (0.25 *M*), 2 g. of potassium iodide was added,

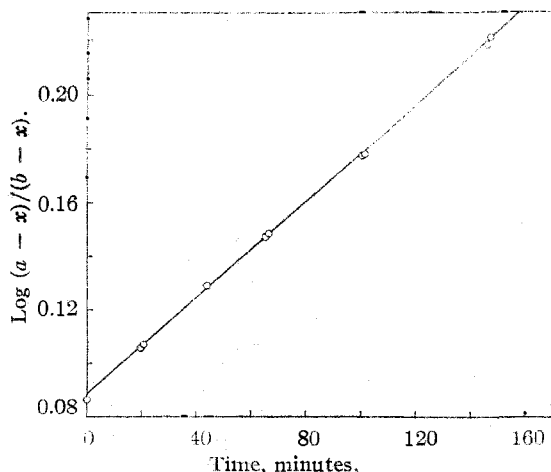


Fig. 1.—Iodination of Pyrrole I; data from Table I.

and the excess arsenite ion was titrated with standard iodine solution.

If the *pH* is too low, some iodine is used during the back titration to iodinate the pyrroles, particularly the α -free pyrroles. If the *pH* is too high, the titration of arsenite ion is inaccurate, as shown by Washburn.¹¹

Second order velocity constants were determined by the equation

$$k_{\text{obs.}} = \frac{2.303}{(a-b)t} \log \frac{b(a-x)}{a(b-x)} \quad (1)$$

in which *a* and *b* are the initial concentrations of pyrrole and titratable iodine, and *x* is the concentration of iodo-pyrrole. $\log(a-x)/(b-x)$ was plotted against time, and $k_{\text{obs.}}$ was determined by the slope of the straight line, after converting the time to seconds.

$$k_{\text{obs.}} = 2.303/(a-b) \text{ (Slope)} \quad (2)$$

Tables I and II give the data for two typical experiments. The apparent drift in velocity constant calculated from the data in Table I is due to the initial heating of mixing. This is shown by Fig. 1. Figures 1 and 2 are plots of $\log(a-x)/(b-x)$ against time and show the straight lines required for a second order equation. Table IV summarizes the data for the iodination of the four pyrroles. Second order velocity constants were determined for different concentrations of iodide ion.

TABLE I

Reaction of Pyrrole I: $[I^-] = 0.805$, $[I_2^-]_0 = a = 0.00672$, $[Py]_0 = b = 0.00551$	
Time, min.	10^3x
0	0
19.5	114
20.7	117
43.7	198
44.7	198
65.3	250
66.3	253
100.2	312
101.3	312
146.0	366
147.0	369

$k_{\text{obs.}} = 0.0280$ liters per mole sec. (by graphical solution)

TABLE II

Reaction of Pyrrole III: $[I^-] = 0.857$, $[I_2^-]_0 = a = 0.00921$, $[Py]_0 = b = 0.00580$	
Time, min.	10^3x
0	0
232	59
233	58
283	74
555	137
556	137
1062	224
1063	223
1614	289
1615	290

$k_{\text{obs.}} = 0.00096$ liter per mole sec. (graphical solution)

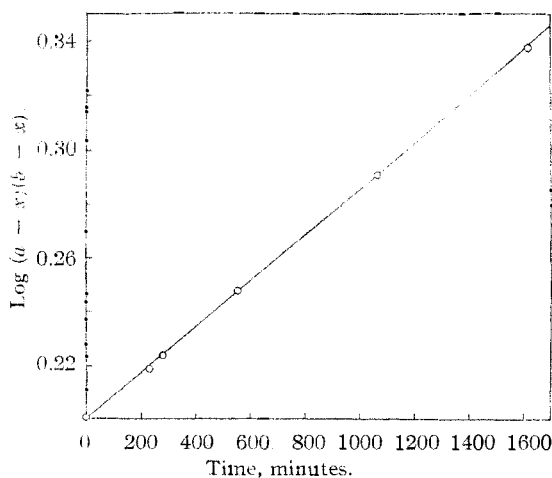


Fig. 2.—Iodination of Pyrrole III; data from Table II.

(11) Washburn, THIS JOURNAL, 30, 31 (1908).

Rates of Reduction of Iodopyrroles with Hydriodic Acid.—A solution of the iodopyrrole to be examined (0.200 g. in 20.0 cc. of purified dioxane) was added to 10.0 cc. of water containing 1.5 g. of potassium iodide. The reaction was started by the addition of 1.00 cc. of 2.0 *N* hydrochloric acid. At intervals, 5.00-cc. samples were pipetted into 10 cc. of water saturated with potassium iodide and containing 1 g. of sodium acetate. The reaction is made extremely slow by the excess sodium acetate, while the iodination is checked by the large excess of iodide ion. If the iodine is titrated immediately by sodium thiosulfate, consistent results can be obtained. The data for two experiments are given in Table III.

TABLE III
REDUCTION OF PYRROLES

I ⁻ = <i>a</i> = 0.0645, [Py] ₀ = <i>b</i> = 0.0210, [H Solv ⁺] ₀ = <i>c</i> = 0.292 Pyrrole	Time, min.	I ₃ ⁻ = <i>x</i>
V	0	0
	4	0.0036
	174	.0192
	666	.0211
		<i>k</i> = 0.0140 (l. ² /mole ² sec.)
VI	0	0
	11	0.0003
	183	.0042
	661	.0101
	1573	.0153
		<i>k</i> = 6.87 × 10 ⁻⁴ (l. ² /mole ² sec.)

The reduction of pyrrole VI, for which more points are available, follows a third order rate equation closely and the plot extrapolates to zero time. The reduction of pyrrole V is assumed to obey the same law. Because of the speed of this reaction, there was a marked heating effect on mixing and the plot extrapolates to -212 seconds.

Synthesis of α - and β -Free Pyrroles.—These pyrroles were synthesized by the method of Corwin and Quattlebaum.¹² They were recrystallized from methanol at Dry Ice temperature and were dried under vacuum. Dioxane solutions were prepared, which were kept frozen until they were used.

Synthesis of 2-Iodo-3,5-dimethyl-4-carbethoxypyrrole, and 3-Iodo-2,4-dimethyl-5-carbethoxypyrrole.—These compounds were prepared by the method of Fischer.^{10b}

Synthesis of 2-Iodo-1,3,5-trimethyl-4-carbethoxypyrrole.—Two grams of 1,3,5-trimethyl-4-carbethoxypyrrole was dissolved in 25 cc. of methanol, and water was added until precipitation began. The theoretical amount of iodine was dissolved in a minimum of alcohol and added over a period of several minutes to the pyrrole solution. Several grams of sodium bicarbonate was added. After twenty minutes, water was added to complete the precipitation of the iodopyrrole. The iodopyrrole was decolorized with bone black and recrystallized twice from methanol at Dry Ice temperature; yield, 78%, m. p. 103.0-103.5°.

Anal. Calcd. for C₁₀H₁₄O₂N₂: C, 39.11; H, 4.59. Found: C, 39.28; H, 4.22.

Synthesis of 3-Iodo-1,2,4-trimethyl-5-carbethoxypyrrole.—This iodopyrrole was synthesized from 1,2,4-trimethyl-5-carbethoxypyrrole in a manner similar to that described above for its isomer; yield, 75%, m. p. 87°.

Anal. Calcd. for C₁₀H₁₄O₂N₂: C, 39.11; H, 4.59. Found: C, 39.36; H, 4.53.

Reduction of Iodopyrroles by Hydriodic Acid.—The following experiment is typical of the reduction of an α -iodopyrrole to the corresponding α -free pyrrole. 2-Iodo-1,3,5-trimethyl-4-carbethoxypyrrole (1.8 g.), potassium iodide (1.0 g.), glacial acetic acid (5.0 cc.) and sodium

bisulfite (1.5 g.) were added to 75 cc. methanol (80%) in an erlenmeyer flask, the flask was stoppered, and the mixture was allowed to stand overnight. The solution was evaporated under vacuum until the pyrrole began to precipitate. Water was added to complete the precipitation. The product was recrystallized from methanol at Dry Ice temperature; yield, 75%, m. p. 59-60°, mixed m. p. with 1,3,5-trimethyl-4-carbethoxypyrrole, 59-60°.

The β -iodopyrroles were less reactive and required hydrochloric acid instead of acetic acid. The sodium bisulfite is necessary to destroy free iodine as fast as it is formed and drive the reaction to completion. That the bisulfite ion (or sulfur dioxide) is not the reducing agent was demonstrated in an experiment in which the potassium iodide was omitted.

Discussion

The Mechanism of Iodination of Pyrroles.—The fact that the velocity of iodination of pyrroles is greatly dependent upon the concentration of iodide ion leads to the following considerations which best explain the observed results. Iodide ion and free iodine are in equilibrium with triiodide ion.

$$K = (I_2)(I^-)/(I_3^-) \quad (3)$$

This equilibrium constant in water can be calculated from the data of Jones and Kaplan.¹³ For the temperature 26.5° we have used the value, $K = 0.00145$. This should be close to the correct value in dioxane-water because of the equivalence of charge in numerator and denominator. If the concentration of iodide ion is large compared with that of titratable iodine, then the liberation of iodide ion during the iodination reaction will change the concentration of iodide ion by a negligible amount, and it may be considered to be a constant. If the iodination is an electrophilic one, then triiodide ion will be repelled by negative centers in the pyrrole ring, and will not react, or will react at a specific rate much lower than that for the reaction with free iodine, the concentration of which is determined by the above equilibrium.

The appropriate kinetic equation is¹⁴:

$$\frac{dx}{dt} = \frac{k_2K}{K + (I^-)} (a - x)(n - x) \quad (4)$$

If we substitute

$$k_{obs.} = k_2K/(K + I^-) \quad (5)$$

this becomes the ordinary second order equation, which integrates to eqn. 1.

If K is considered to be small compared to (I^-) then

$$k_{obs.} = \frac{k_2K}{(I^-)} \text{ or } k_{obs.}(I^-) = k_2K = \text{constant} \quad (6)$$

Equation 6 thus requires that the experimentally observed velocity constant multiplied by the iodide ion concentration be a constant for each pyrrole. Table IV shows that the relationship holds fairly well. There is, however, a drift

(13) Jones and Kaplan, *ibid.*, **50**, 1845 (1928).

(14) Soper and Smith, *J. Chem. Soc.*, 2757 (1927); Bartlett and Tarbell, *This Journal*, **58**, 446 (1936).

upwards as the concentration of iodide ion becomes small.

TABLE IV
IODINATION OF PYRROLES

Pyrr-ole	I ₂ added	(I ⁻)	[Py] ₀	k _{obs.}	(I ⁻) ^x k _{obs.}	k ₂ ^a
I	0.00672	0.805	0.00551	0.0280	0.0225	15.5
	.00827	.696	.00777	.0326	.0227	15.6
	.00827	.696	.00563	.0328	.0228	15.7
	.00850	.497	.00638	.0467	.0232	16.0
II	.00651	.805	.00853	.0296	.0238	16.4
	.00580	.600	.00990	.0412	.0246	17.0
	.00679	.518	.00948	.0485	.0251	17.3
III	.00921	.857	.00580	.00096	.00083	0.57
	.00662	.676	.00513	.00135	.00091	0.63
	.00578	.600	.00513	.00150	.00090	0.61
	.00568	.400	.00580	.00280	.00112	(0.77)
IV	.00788	.600	.00622	.00167	.00100	0.69
	.00853	.497	.00622	.00201	.00100	0.69
	.00568	.400	.00550	.00300	.00120	(0.83)

^a Liters per mole sec.

This drift may be caused by some reaction of hypiodous acid with the pyrrole. Li¹⁵ showed that in the iodination of tyrosine by iodine solutions containing a low concentration of iodide ion (less than 0.10 molar) the observed second order constant obeys the following relationship

$$k_{\text{obs.}} = \frac{A}{(I^-)^2} + \frac{B}{(I^-)}$$

The first term is due to the reaction of hypiodous acid, the second due to reaction by free iodine. At very low concentrations of iodide ion, the first term is very important. At higher concentrations of iodide ion, the second term increases in importance, and will eventually become much larger than the first term. Then, $k_{\text{obs.}} = B/I^-$, which is eqn. 4, in which $B = k_2K$. In the experiments reported here, the concentrations of iodide ion were much higher than in the experiments of Li (0.40–0.86 *M*, compared with 0.03–0.10 *M*), so that eqn. 4 is obeyed fairly well. Free iodine thus is shown to be the principal iodinating agent under the conditions of these experiments.

Details of Mechanism.—Sidgwick, Taylor and Baker¹⁶ have expressed the belief that the great reactivity of pyrroles in both an α and a β -position may be due to their ability to assume pyrrolenine structures.



This view has been opposed by Brunings and Corwin.¹⁷ The similar kinetics of iodination of both N-methyl and N-H pyrroles is consistent with that expected for typical electrophilic reactions. It is impossible for the N-methyl pyrroles to assume a pyrrolenine structure without the migration of a methyl group. Since they can be iodinated without a change in the carbon skeleton

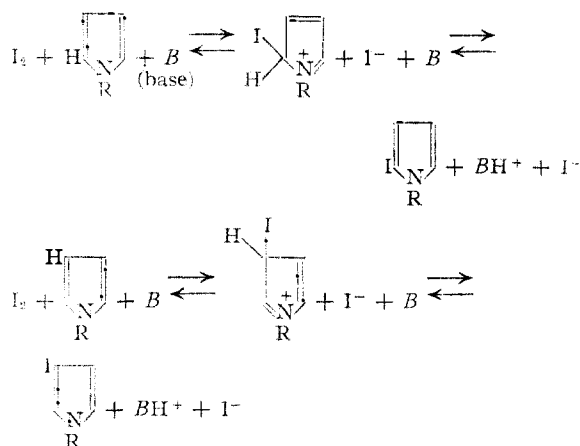
(15) Li, *ibid.*, **64**, 1147 (1942).

(16) Sidgwick, Taylor and Baker, "The Organic Chemistry of Nitrogen," Oxford, 1937, pp. 482-490.

(17) Brunings and Corwin, *THIS JOURNAL*, **64**, 594 (1942).

by a reaction which is reversible, it is extremely unlikely that a pyrrolenine intermediate is involved.

The facts of the forward and reverse reactions presented below are consistent with a mechanism involving an ionic intermediate, in which the first step is rate-determining:



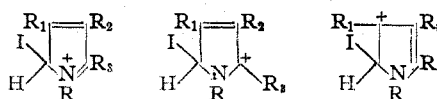
Relationship Between Structure and Reactivity. (a) **The Effect of N-Methyl.**—The specific velocity constants for the iodination of the four pyrroles were estimated by the use of eqn. 6. The value of $K = 0.00145$ was used, although it may be somewhat in error. However, this does not affect the relative velocity constants. The averages of these constants (from Table IV, neglecting those for the experiments with the lowest concentration of iodide ion) are recorded in Table V.

TABLE V

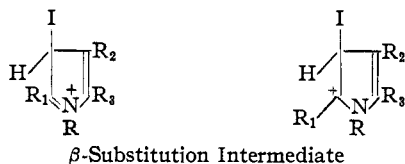
Pyrrrole	k (l. per mole sec.)	Ratios
I N-H, α -H	15.7	I/III 26.2
II N-CH ₃ , α -H	16.9	II/I 1.08
III N-H, β -H	0.60	IV/III 1.15
IV N-CH ₃ , β -H	0.69	II/IV 24.5

The results in Table V show that in both cases N-methylation has slightly increased the reactivity, although the differences are small. The N-methyl group thus increases the reactivity of pyrroles to a much smaller extent than a methyl group increases the reactivity of the benzene ring.

(b) **The Effect of Position.**—Table V shows that the α -free pyrroles are much more reactive than the β -free pyrroles. The ionic intermediate mechanism is consistent with this relationship, since the intermediate in α -substitution is stabilized by three resonance forms while that in β -substitution is stabilized by only two forms.



α -Substitution Intermediate



Iodopyrroles as "Positive Halogen" Compounds.—The results in Table III on the reaction of two iodopyrroles with hydriodic acid are shown graphically in Fig. 3. The α -iodopyrrole is shown to be twenty times as reactive as the β -iodopyrrole. A difference of 24.5-fold was observed for the iodination of the corresponding unsubstituted pyrroles II and IV in Table V. This suggests a mechanism in which a proton attacks an electron pair, forming the same ionic intermediate present in the iodination, which then reacts with an iodide ion to form free iodine. The factors which determine the reactivity toward iodine also determine the reactivity toward a proton in the reverse reaction.

The iodopyrroles thus belong to class of "positive halogen" compounds, discussed by Bartlett and Tarbell and Altschul and Bartlett.¹⁸ In compounds of this type, a halogen atom may be transferred as a positive group from one compound to another in a manner similar to that in which a proton is transferred. The iodine atom simultaneously loses an electron pair and shares another pair in both the forward and the reverse reaction, and probably does not exist as a positive atom.

The Iodination Equilibrium.—The estimation of the forward and reverse velocity constants permits an approximation to the magnitude of the equilibrium constant of the iodination reaction to be made. The constant

$$K = \frac{[RI][HSolv^+][I^-]}{[RH][Solv][I_2]}$$

is approximately 24 for the α iodination and 21 for the β , assuming the solvent to be 48.2 molar. The ratio of equilibrium constants is thus about 1.1 while the corresponding ratio of rate constants is 24.5. This is clearly a case in which rate constants and equilibrium constants are not parallel. A possible explanation is that the attacking reagents in both directions are sufficiently similar that a structural change which affects the rate of

(18) Bartlett and Tarbell, *THIS JOURNAL*, **58**, 466 (1936); Altschul and Bartlett, *J. Org. Chem.*, **5**, 622 (1941).

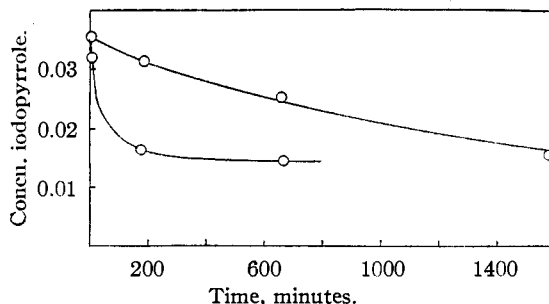


Fig. 3.—Reduction of iodopyrrole; data from Table III; upper curve, Pyrrole VI; lower curve, Pyrrole V.

reaction of the unsubstituted pyrrole affects that of the iodopyrrole almost equally.

One of us, K.W.D., wishes to acknowledge a grant-in-aid from the Hynson, Westcott and Dunning Research Fund.

Summary

1. The kinetics of iodination of four similar pyrrole derivatives have been studied.
2. The rates of these reactions are dependent upon the concentration of the pyrrole derivative and of the free iodine in the solution.
3. The kinetics indicate that still another species, perhaps hypoiodous acid, is active in iodination.
4. The α -position is found to be about 25 times as reactive as the β position in the pyrrole ring.
5. N-Methyl groups increase the reactivity of the pyrrole ring by 8–15%.
6. This effect is much smaller than the effect of methyl on the reactivity of benzene.
7. Iodopyrroles can be reduced to pyrroles with hydriodic acid.
8. The α position is approximately twenty times as reactive to hydrogen iodide reduction as the β position.
9. Rough values for the equilibrium constant of the iodination reaction have been obtained in two cases.
10. This equilibrium constant is little affected by a structural change in the pyrrole.
11. The significance of these findings with respect to the mechanism of the iodination reaction is discussed.