of 5-(*o*-nitrobenzylidene)-hydantoin (XII) in 50 ml. Heating the mixture on a steam-bath caused evolution of hydrogen chloride. From this solution there was obtained 0.65 g. (73% yield) of the colorless dichloro derivative of 5-(*o*-nitrobenzylidene)-hydantoin (XII), m.p. 178–180° dec.

**Ozonolysis of XIII.**—An ozone–oxygen mixture was passed through a solution of the monochloro derivative (0.35 g.) in 50 ml. of ethyl acetate; ozone was detectable in the effluent gas within 5 minutes; the solution had lost its original light yellow color after about 2 hours of gasification. Zinc dust and ice-water were added, the mixture was filtered; the filtrate yielded 130 mg. of *o*-nitrobenzoic acid (m.p. 145–146°) and 10 mg. of parabanic acid, m.p. 241–243° dec.

**Difference in Activity of Halogen Atoms in the Dichloro-5-(*o*-nitrobenzylidene)-hydantoin (XII).** A.—To 0.31 g. (0.001 mole) of II in 25 ml. of acetone was added 0.065 g. (0.001 gram-atom) of powdered zinc and the mixture was refluxed for 24 hours. The hot solution was filtered and the filtrate was shown to contain chloride ions; the solvent was evaporated from the filtrate. The residue was recrystallized from diluted alcohol to give 0.20 g. (67% yield) of 5-(α-chloro-*o*-nitrobenzylidene)-hydantoin (XIII).

B.—One-half gram of XII in 50% acetic acid solution was treated with one gram of potassium iodide; almost immediately, iodine was liberated. The solution was steam distilled and the residue concentrated to about 10 ml. before being ether extracted. After two recrystallizations from benzene, there was obtained 0.2 g. of crystals XIV, m.p. 144.0–145.5°.

*Anal.* Calcd. for $C_{10}H_6ClN_3O_4$: Cl, 13.25; N, 15.70. Found: Cl, 12.88; N, 15.83.

This material dissolved unaltered in 0.2 *N* sodium hydroxide solution and was inactive toward concentrated ammonium hydroxide solution. It did not exhibit any degree of unsaturation. A mixture of XIV with the higher-melting monochloro-5-(*o*-nitrobenzylidene)-hydantoin of m.p. 245–246° dec. melted over the range 126–135°; after cooling to a solid, upon reheating the mixture melted at 122–142°.

C.—In a repetition of experiment B, the higher melting geometrical isomer XIII was obtained and no evidence of presence of the lower-melting isomer XIV could be found.

**Preparation of 5-(α-Mercapto-2-nitrobenzylidene)-hydantoin. A. From the Higher Melting Monochloro-5-(*o*-nitrobenzylidene)-hydantoin (XIII).**—To a solution of 1.05 g. (0.016 mole) of potassium hydroxide which had been saturated with hydrogen sulfide at 0°, was added 0.22 g. (0.00082 mole) of XIII and the solution was refluxed for one hour. The red solution was cooled, acidified with glacial acetic acid and refrigerated to precipitate solid material. The latter was removed and recrystallized from diluted alcohol; yield 0.16 g. (74%), m.p. 125–126°.

*Anal.* Calcd. for $C_{10}H_7N_3O_4S$: N, 15.85. Found: N, 15.82.

B. **From the Lower Melting Monochloro-5-(*o*-nitrobenzylidene)-hydantoin (XIV).**—Using the above procedure, 0.22 g. of XIV yielded 0.18 g. (83%) of the same sulfur derivative, m.p. 123–125°.

C. **From the Bromo Derivative of 5-(*o*-Nitrobenzylidene)-hydantoin (XI).**—In an analogous manner, 0.50 g. of XI, 2.10 g. of potassium hydroxide in 16 ml. of water saturated with hydrogen sulfide upon heating produced 0.36 g. (85% yield) of the crude sulfur product, m.p. 121–124°.

**Ultraviolet Absorption Spectra of Solutions of Derivatives of 5-(*o*-Nitrobenzylidene)-hydantoin.**—A Beckman Model DU Spectrophotometer was used to obtain the absorption spectra of ethyl alcoholic solutions of α-nitro, α-bromo, α-chloro, 3,α-dichloro and α-mercapto derivatives. All of these compounds exhibited maximum absorption at 275 mμ, and a minimum at 250 mμ. However, whereas the spectra of these compounds were highly similar in appearance the absorption spectrum of the mercapto derivative was quite easily recognized because of its lesser tendency to absorb.

AUSTIN, TEXAS

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

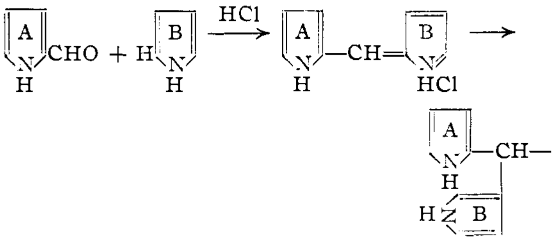
# Kinetics of the Condensation of Dipyrrylmethenes with an α-Free Pyrrole[1]

BY ALSOPH H. CORWIN AND KENNETH W. DOAK[2]

RECEIVED JULY 22, 1954

In a condensation with an α-free pyrrole, a dipyrrylmethene appears to be an electrophilic reagent. Substituents which make the bridge carbon more positive increase the rate of condensation. The rate depends on the concentrations of both the α-free pyrrole and the dipyrrylmethene. In a catalyzed reaction in benzene, monomeric acetic acid is the principal catalytic species at very low concentrations, while the dimer apparently becomes important at higher concentrations. Hydroxydipyrrylmethenes are very unreactive toward an α-free pyrrole, because of an unfavorable equilibrium. This alters the course of the aldehyde synthesis of dipyrrylmethenes from an N-methylpyrryl aldehyde and α-free pyrrole, so that two mono-N-methyldipyrrylmethenes have been isolated for the first time.

The mechanism of the aldehyde synthesis of dipyrrylmethenes has been studied by Corwin and Andrews,[3] and by Paden, Corwin and Bailey.[4] The condensation of a pyrryl aldehyde and an α-free pyrrole does not always give the expected dipyrrylmethene. The dipyrrylmethene formed may react further with the α-free pyrrole to form a tripyrrylmethane, which can undergo cleavage to form a different dipyrrylmethene and α-free pyrrole. Further condensations and cleavage may occur, so that three dipyrrylmethenes are possible, two symmetrical and one unsymmetrical. Corwin and Andrews,[3a] by changing substituents on the pyrrole nuclei, were able to isolate all three types of dipyrrylmethenes. This mechanism accounts for the failure of several attempts to synthesize a mono-N-methylmethene by the aldehyde synthesis.[3b]



This synthesis thus involves several competing reactions. The product isolated will be determined by the relative velocities of the competing reactions. Therefore, to determine the effects of sub-

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[1] Studies in the Pyrrole Series XXV. Paper XXIV, G. G. Kleinspehn and A. H. Corwin, THIS JOURNAL, **76**, 5641 (1954).

[2] The William R. Warner and Co., Inc., Fellow, The Johns Hopkins University. Acknowledgment is also gratefully made to the Hynson, Westcott and Dunning Research Fund for a grant-in-aid

[3] (a) A. H. Corwin and J. S. Andrews, THIS JOURNAL, **58**, 1086 (1936); (b) **59**, 1973 (1937).

[4] J. H. Paden, A. H. Corwin and W. A. Bailey, Jr., *ibid.*, **62**, 418 (1940).

stituents, rates of condensation were measured for five dipyrrylmethenes. These have the same substituents on one ring, but different substituents on the other ring (Chart I). The α-free pyrrole was 3,5-dimethyl-4-carbethoxypyrrole (VI). In one experiment the N-methyl analog of VI was studied.

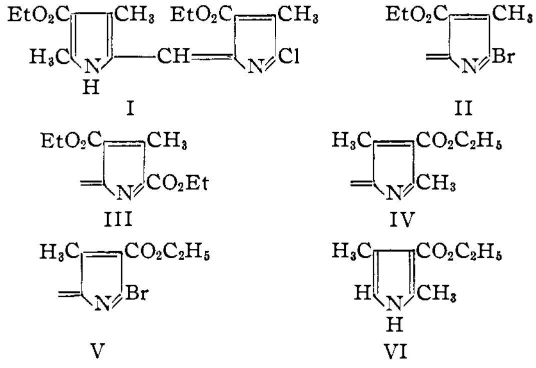

CHART I

Paden, Corwin and Bailey[4] demonstrated qualitatively that III is much more reactive than IV in a condensation with pyrrole VI.

Acetic acid was found to catalyze the reaction, although it is much less reactive than hydrogen chloride. No catalyst was required for dipyrrylmethene III.

## Discussion

**Kinetics of the Catalyzed Reaction.**—The rate of condensation of dipyrrylmethenes with α-free pyrrole VI is second-order at any concentration of acetic acid, depending on concentration of pyrrole and dipyrrylmethene. Presumably both monomeric (M) and dimeric (D) forms of acetic acid act as catalyst, so the rate follows the expression

$$\text{rate} = [k_M(\text{M}) + k_D(\text{D})](\text{pyrrole})(\text{methane}) \quad (1)$$

in which the experimental rate constant is

$$k_{\text{exp}} = k_M(\text{M}) + k_D(\text{D}) \quad (2)$$

The values for $k_M$ and $k_D$ are determined as

$$(\text{D}) = K(\text{M})^2 \quad (3)$$

in which $K$ is the equilibrium constant, and assumed to be $4.2 \times 10^3$ at 25°.[5]

$$(\text{HOAc}) = 2(\text{D}) + (\text{M}) \quad (4)$$

Substitution of 3 into 4

$$2K(\text{M})^2 + (\text{M}) - (\text{HOAc}) = 0 \quad (5)$$

$$(\text{M}) = \frac{\sqrt{8K(\text{HOAc}) + 1} - 1}{4K} \quad (6)$$

and

$$(\text{D}) = \frac{(\text{HOAc}) - (\text{M})}{2} \quad (7)$$

$k_M$ and $k_D$ are determined by substituting experimental values into 2. These values can be used to calculate rate constants ($k_{\text{calcd.}}$) for various concentrations of acetic acid shown in Table I. For dipyrrylmethene II, $k_{\text{expt.}}$ and $k_{\text{calcd.}}$ check best for $k_M = 41$ and $k_D = 9.0$. For dipyrrylmethene IV the best fit is obtained for $k_M = 185$ and $k_D = 61$. No calculations were made for dipyrrylmethenes I and V, which were studied over a more narrow range of acetic concentration. The experimental constants are given in Table I.

TABLE I

RATES OF ACETIC ACID-CATALYZED CONDENSATION OF DIPYRRYLMETHENES WITH 3,5-DIMETHYL-4-CARBETHOXYPYRROLE IN BENZENE

| $10^3C^a$ | $10^3$(M) | $10^3$(D) | $k_{\text{expt.}}{}^b$ | $k_{\text{calcd.}}$ |
|---|---|---|---|---|
| | | Methene II | | |
| 54.6 | 2.49 | 26.1 | 0.328$^c$ | 0.334 |
| 27.5 | 1.75 | 12.9 | .185 | .188 |
| 5.46 | .75 | 2.36 | .051 | .052 |
| 2.75 | .516 | 1.12 | .034 | .031 |
| 1.37 | .349 | .510 | .0178 | .0189 |
| .68 | .232 | .223 | .0107 | .0116 |
| .140 | .083 | .057 | .0032 | .0038 |
| .000 | ... | ..... | .0015$^d$ | |
| .000 | ... | ..... | .00044$^e$ | |
| | | Methene IV | | |
| 5.46 | 0.75 | 2.36 | 0.289 | 0.283 |
| 2.75 | .516 | 1.12 | .169 | .164 |
| 1.37 | .349 | .510 | .094 | .096 |
| .80 | .255 | .273 | .067 | .064 |
| .50 | .192 | .152 | .043 | .045 |
| .088 | .059 | .0145 | .0121 | .0118 |
| .044 | .035 | .0045 | .0069 | .0068 |
| .000 | ... | ..... | .0032$^d$ | |
| .000 | ... | ..... | .0017$^e$ | |

| $10C^a$ | $k_{\text{expt.}}$ | $10^3C^a$ | $k_{\text{expt.}}$ |
|---|---|---|---|
| Methene I | | Methene V | |
| 8.85 | 0.0344 | 8.85 | 1.83 |
| 5.90 | .0255 | 5.90 | 1.38 |
| 2.95 | .0147 | 2.95 | 0.76 |
| 0.00 | .00031$^e$ | 1.48 | .37 |
| | | 0.00 | .015$^d$ |

$^a$ $C$ = (HOAc). Concentrations in moles/liter. $^b$ Liters/mole sec. $^c$ Estimated from slope of plot of log $(a - x/b - x)$. $^d$ In C.P. benzene. $^e$ Benzene distilled from sodium, then containing half the saturation concn. of water.

When (HOAc) is relatively large, so that $8K(\text{HOAc}) >> 1$

$$k_{\text{expt}} = C_1(\text{HOAc}) + C_2\sqrt{(\text{HOAc})} \quad (8)$$

in which the constants $C_1$ and $C_2$ are $(2k_M - k_D)/\sqrt{8K}$ and $k_D/2$, respectively. When (HOAc) is very large, the linear term in 8 predominates. The relationship can be shown to fit the data fairly well, except at the lower concentrations of acetic acid.

**Effect of Structure of the Dipyrrylmethenes.**—The relative reactivities of dipyrrylmethenes I, II, IV and V were estimated from the slopes of plots of rate constant *vs.* concn. of acetic acid in the range 0.003 to 0.006 *M*. This method probably is more reliable than a comparison of the rate constants for the uncatalyzed reaction, which were quite erratic. However, dipyrrylmethene III, which required no catalyst, can be compared with these only by uncatalyzed constants. The constants (uncatalyzed) for I, II and IV were measured simultaneously in the same sample of solvent. The results are summarized in Table II.

These dipyrrylmethenes differ onlyin the substituents, or position of substituents, in one pyrrole

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[5] H. A. Pohl, M. E. Hobbs and P. N. Gross, *J. Chem. Phys.*, **9**, 408 (1941).

TABLE II

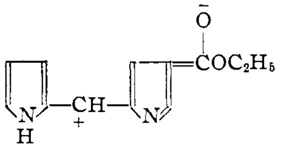
RELATIVE REACTIVITIES OF DIPYRRYLMETHENES

| Methene | Rel. react.[a] | Uncatalyzed constants | $\lambda_{max.}$, Å. Base | Salt |
|---|---|---|---|---|
| I | 1.00 | 0.00031 | 4870 | 5020 |
| II | 1.81 | .00044 | 4910 | 5050 |
| III | ... | .085 | 4280 | 4840 |
| IV | 11.3 | .0017 | 4500 | 4700 |
| V | 57 | .015 | 4400 | .. |
| VIII | ... | ..... | 4430 | 4620 |
| | | | 3700 | .. |

[a] From slopes of *k vs.* acetic acid concn.

ring. Methene V is 5.0 times as reactive as IV, showing that substitution of a bromine for a methyl group has increased the reactivity. Comparison of I and II shows that bromine in place of chlorine in the 5′-position makes the system nearly twice as reactive.

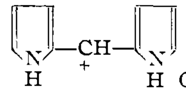
Methene V is 31 times as reactive as II, although they differ in structure only by a reversal of positions for a methyl and a carbethoxy group on the 3′- and 4′-positions of one pyrrole ring. Electronic effects of the carbethoxy group on the bridge carbon should be similar for both β-positions. A resonance structure can be written for each, with a positive charge on the bridge carbon and negative charge on the carbonyl oxygen.



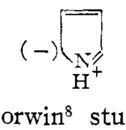
However, the carbethoxy group in the 3′-position should offer much more steric hindrance to the approach of the α-free pyrrole to the bridge carbon, causing a lower reactivity.

Dipyrrylmethene III, based on the rates of the condensations in the absence of acetic acid, has a reactivity at least 200–300 times as great as that for I or II.[6] It differs only in the substitution of a carbethoxy group for chlorine or bromine in the 5′-position. This group can introduce an additional resonance structure with a positive charge on the bridge carbon, in a manner similar to that for a 3′- and 4′-carbethoxy group.

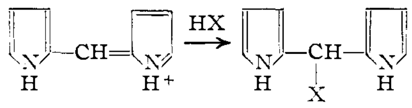
It thus appears that the dipyrrylmethene is an electrophilic reagent, since its reactivity is increased by groups which are expected to make the bridge carbon more positive. α-Free pyrroles are believed to be nucleophilic agents in some substituted reactions, such as iodination.[7] Catalysis by acetic acid should make possible the formation of small amounts of the dipyrrylmethene salt as an intermediate which can form a polarized structure with a positively bridged carbon.



This structure may be represented as reacting with the polarized pyrrole structure

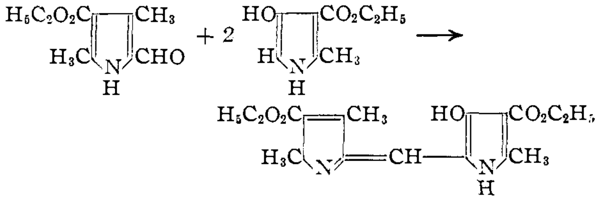


Brunings and Corwin[8] studied the structural factors which influence the tendency of the dipyrrylmethene system to form the covalent system.



Increasing the number of carbethoxy groups, which make the bridge carbon more positive, or increasing the basicity of $X^-$, increases the tendency to form the covalent structure. Dipyrrylmethene III forms the stable carbinol ether. Similar structural factors thus appear to govern both reactions of the dipyrrylmethene system.

**Effect of a Hydroxyl Group upon the Equilibrium of the Condensation.**—Fischer and Heyse[9] attempted to synthesize a dihydroxytripyrrylmethane by the Feist fusion. They condensed one mole of a pyrryl aldehyde with two moles of a hydroxy-α-free pyrrole, but obtained a hydroxydipyrrylmethene VII, which presumably does not condense with the α-free pyrrole.



VII

If the hydroxyl group is replaced by methyl, the tripyrrylmethane is formed.

A hydroxydipyrrylmethene (VIII, Chart II) was prepared, which should be more reactive than VII, since it has an additional carbethoxy group. It differs from III, the most reactive dipyrrylmethene studied, only by replacement of a methyl group by hydroxyl. It showed no condensation with α-free pyrrole VI under conditions that would cause rapid condensation of III.

The equilibrium appears to be unfavorable for the condensation. Thus the expected tripyrrylmethane X should also be formed from dipyrrylmethene III and 3-hydroxy-4-carbethoxy-5-meth-

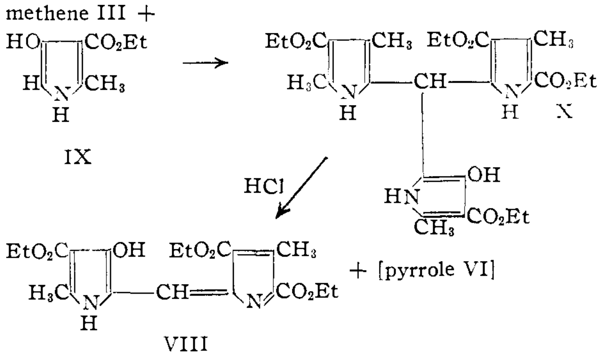


CHART II

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(6) The difference may be greater, since the uncatalyzed velocity constants for I and II appeared to be lower in benzene freshly distilled from sodium.

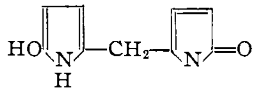
(7) K. W. Doak and A. H. Corwin, THIS JOURNAL, **71**, 159 (1949).

(8) K. J. Brunings and A. H. Corwin, *ibid.*, **66**, 337 (1944).

(9) H. Fischer and M. Heyse, *Ann.*, **439**, 256 (1924).

ylpyrrole (IX). They readily condense to form an intermediate, presumably tripyrrylmethane X, which is cleaved readily by HCl to form dipyrrylmethene VIII (Chart II).

A hydroxyl group presumably makes the bridge carbon more negative. This view is supported by the fact that four so-called dihydroxydipyrrylmethenes are reported to have the methane structure.[10] Two hydroxyl groups presumably make the bridge carbon more basic than the oxygen or nitrogen. The effect is opposite to that of carbethoxy groups,



which facilitate methane formation by contributing to the positive character of the bridge carbon.

**Effect of a Hydroxyl Group on the Mechanism of the Aldehyde Synthesis.**—Corwin and Andrews[3] attempted to synthesize mono-N-methylmethenes by the aldehyde synthesis. In one case, the symmetrical dipyrrylmethene IV was the product, which resulted from a cleavage of a tripyrrylmethane intermediate.[3a] In the other case, the tripyrrylmethane XIII was isolated, which was cleaved with difficulty to dipyrrylmethene IV[3b] (Chart III). In both cases, the anticipated dipyrrylmethene, if formed at all, condensed rapidly with the α-free pyrrole to form a tripyrrylmethane, which cleaved to give the abnormal product.

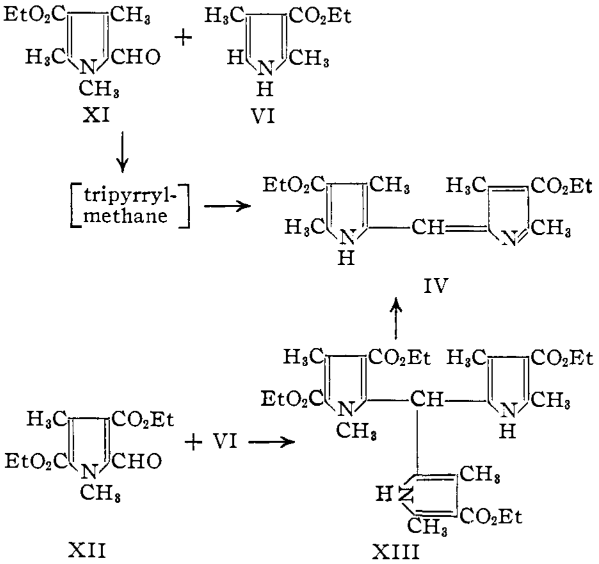


CHART III

If the structures of the pyrroles are such that the expected dipyrrylmethene does not condense with the α-free pyrrole, then the synthesis should follow a normal course, and it should be possible to obtain a mono-N-methylmethene. Since a hydroxyl group in dipyrrylmethene VII and VIII makes the system unreactive to an α-free pyrrole, the pyrryl aldehydes XI and XII should react with 3-hydroxyl-4-carbethoxy-5-methylpyrrole IX in the normal manner. The condensations in both cases stopped with the formation of the desired mono-N-methyldipyrrylmethenes, XIV and XV (Chart IV).

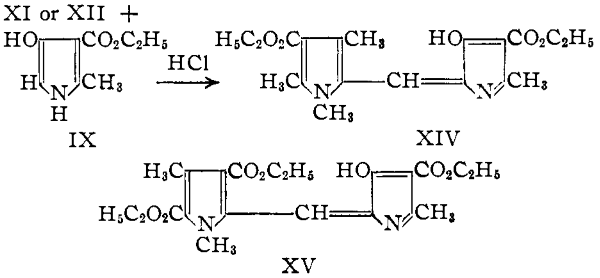


CHART IV

The absorption spectra of these methenes, to be reported in a subsequent publication, suggest that they actually may have a ketone structure, which may influence their reactivity.

**Relation Between Chemical Reactivity and Absorption Spectra.**—Brooker and co-workers[11] have suggested that a cyanine dye which absorbs nearer the infrared has a higher resonance energy, and hence is less reactive, than one which absorbs nearer the ultraviolet. In one example, they demonstrated that this is correct.

By Brooker's criterion, the reactivity of the dipyrrylmethenes is expected to increase with decreasing wave length. Table II shows relative reactivities, together with absorption maxima, for both the free bases and salts. With the exception of dipyrrylmethene VII, there is a fair qualitative order between relative reactivities and absorption maxima for the free bases. However, four of the dipyrrylmethenes required an acid catalyst, suggesting that the salt form is the reactive species. The maxima for the salts do not correlate with relative reactivities.

Presumably reactivity in this condensation is determined by the ease with which the bridge carbon can take a positive charge. Structural changes which make the bridge carbon more positive do not necessarily cause a shift of the absorption maximum to the ultraviolet. Brunings and Corwin demonstrated that the di-N-methyl analog of dipyrrylmethene IV takes a covalent structure more readily than the salt of IV, but has the absorption maximum shifted 400 Å. to the infrared.[12] They believe that the di-N-methyl compound has a lower resonance energy than IV.

**Effect of N-Methylation of the α-Free Pyrrole.**—The N-methyl analog of VI is less reactive toward dipyrrylmethene III than VI by a factor of greater than $10^3$. Paden, Corwin and Bailey[4] suggested a qualitative difference. In an iodination reaction[7] it is slightly more reactive, although the difference is small. Both iodine and the dipyrrylmethene appear to be electrophilic reagents. The polar effect of the N-methyl group tends to increase the reactivity toward an electrophilic reagent, while steric hindrance tends to decrease it. The decreased reactivity toward dipyrrylmethene III, an electrophilic reagent, must then be a result of steric hindrance. In a reaction with the smaller iodine

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(10) (a) F. Pruckner and H. von Dobeneck, *Z. physik. Chem.*, **190A**, 43 (1941); (b) H. von Dobeneck, *Z. physiol. Chem.*, **270**, 223 (1941).

(11) L. G. S. Brooker, F. L. White, G. H. Keyes, C. P. Smyth and P. F. Oesper, THIS JOURNAL, **63**, 3192 (1941).

(12) K. J. Brunings and A. H. Corwin, *ibid.*, **64**, 593 (1942).

molecule, steric effects are less important, and are compensated for by polar effects.

## Experimental Details

**Method of Measuring Reaction Rates.**—Dipyrrylmethenes are colored compounds with absorption bands in the region 4000–5000 Å., while tripyrrylmethanes are colorless. The concentration of a dipyrrylmethene can thus be determined by measuring the light transmission at the absorption maximum. The measurements were made with a Coleman model 10S double monochromator with 30 mμ slit. Transmission ($I/I_0$) was read directly from a Coleman model 310 potentiometer. Square cuvettes, 1.30 cm. thick, matched to ±0.25% were used. Concentrations were determined from $\epsilon$, the extinction coefficient, by use of Beer's law, or from a plot of log $T$ *vs.* concentration, which is a straight line.

The reactions were carried out in benzene at 25.0°. Periodically, 1.0-ml. samples of the reaction mixtures were pipetted into 10.0 ml. of benzene, which was added to the absorption cell. This dilution was sufficient to virtually stop the reaction in nearly all cases. In a few cases readings of transmission were made 3 and 6 minutes after taking the sample, and a small extrapolation was made. The measured concentrations were multiplied by the dilution factor to obtain the actual concentrations in the reaction mixtures. Concentrations of dipyrrylmethenes were chosen so that the transmission values were in the optimum range of the instrument.

**Rates of Acetic Acid Catalyzed Condensations of Dipyrrylmethenes with 3,5-Dimethyl-4-carbethoxypyrrole.**—Dipyrrylmethenes I, II, IV and V were treated with the α-free pyrrole VI in the presence of a wide range of acetic acid concentration, since the rate constants were quite erratic in the absence of added catalyst. Under the conditions of these experiments the dipyrrylmethenes gave absorption curves characteristic of free bases.[13] Data for typical experiments with each dipyrrylmethene are shown in Table III.

TABLE III

CONDENSATIONS OF DIPYRRYLMETHENES WITH 3,5-DIMETHYL-4-CARBETHOXYPYRROLE IN BENZENE[a]

| Methene II | | Methene III | | Methene IV | |
|---|---|---|---|---|---|
| Time | $10^5$(Me) | Time | $10^5$(Me) | Time | $10^5$(Me) |
| 0 | 10.85 | 0 | 19.2 | 00 | 13.7 |
| 41.5 | 8.73 | 3 | 18.4 | 15.5 | 12.23 |
| 146 | 5.50 | 34.5 | 16.0 | 46 | 10.00 |
| 183 | 4.73 | 63.5 | 14.3 | 140 | 5.81 |
| 315 | 2.57 | 117 | 11.3 | 168 | 4.97 |
| | | | | 205 | 3.98 |
| $10^3C = 5.46$ | | $C$ = Zero | | $10^3C = 0.800$ | |
| $10^4a = 15.38$ | | $10^4a = 9.09$ | | $10^4a = 15.38$ | |
| $k = 0.051$ | | $k = 0.085$ | | $k = 0.067$ | |

[a] Temp. 25.0°; time in minutes; (Me) = concn. of methene; $a$ = initial concn. of pyrrole; $C$ = concn. of acetic acid; $k$ is $k_{\text{expt}}$ in liters per mole sec., determined by graphical solution of second-order rate equation.

The rate constants were determined from the slope of a plot of $\log (a - x/b - x)$ *vs.* time. The apparent second order constant, $k$, is $2.303/a - b \times$ slope, in which $a$ and $b$ are initial concn. of pyrrole and dipyrrylmethene, respectively, and $x$ is the amount reacted in time $t$. $b$ was usually 9 to 15 × $10^{-5}$ $M$; $a$ in most cases was 6 to 20 × $10^{-4}$ $M$. In a few cases, in which the reactions were very slow, $a$ was as high as 90 × $10^{-4}$ $M$. In these cases first-order kinetics are observed, and the rate constants were determined from the slope of a plot of log $b$ *vs.* time.

Dipyrrylmethenes I and IV gave straight line plots for all concentrations of acetic acid studied. The bromodipyrrylmethenes II and V, with the higher concn. of acetic acid, gave curves which indicated that the reverse reaction, cleavage of the tripyrrylmethane, occurred. The plots fall off for long reaction times, especially for V at high concn. of acetic acid.

In the absence of acetic acid, the rates for dipyrrylmethenes-I, II and IV were shown to be influenced by the presence of traces of impurities in the benzene. They reacted much slower in benzene freshly distilled from sodium than in benzene saturated with water. In order to obtain comparative data, their reaction rates, recorded in Table II, were measured in the same sample of benzene, which contained one-half the saturation amount of water.

Dipyrrylmethene II sometimes gives an autocatalytic reaction when no catalyst, or very small amounts, are used, presumably because of the liberation of traces of HBr. Solutions of II usually were more reactive after standing several days.

**Preparation of 3,5-Dimethyl-4-carbethoxypyrrole (VI).**—This α-free pyrrole was prepared by the method of Corwin and Quattlebaum.[14] In order to keep it colorless, it was recrystallized from methanol at Dry Ice temperature immediately after synthesis, dried under vacuum, and dissolved in benzene, which was kept frozen until used. The N-methyl analog **1,3,5-trimethyl-4-carbethoxypyrrole**, was prepared similarly.

**Preparation of 3-Hydroxy-4-carbethoxy-5-methylpyrrole.** This was prepared by the method of Benary and Silbermann.[15]

**Comparison of Reactivities of 3,5-Dimethyl-4-carbethoxypyrrole and 1,3,5-Trimethyl-4-carbethoxypyrrole with Dipyrrylmethene III.**—These α-free pyrroles were compared with dipyrrylmethene III, the most reactive one studied. With the N–H α-free pyrrole VI in dry benzene, the second-order constant is 0.085 liter per mole sec. The data are shown in Table III.

An attempt was made to determine a rate constant for the N-methyl analog of VI. The rate of the uncatalyzed reaction is extremely slow. In dry benzene the concn. of III in a 0.0188 $M$ solution decreased from 2.64 × $10^{-4}$ to 2.56 × $10^{-4}$ $M$ in 44 hours. The approximate constant is 1.4 × $10^{-5}$. If traces of water are present, higher apparent constants (*ca* $10^{-4}$) are obtained. The N-methylpyrrole thus appears to be less reactive than the N–H-pyrrole by a factor of $10^3$–$10^4$.

If the reaction is catalyzed, III reacts with acetic acid, the absorption band decreasing in intensity. A 2.10 × $10^{-4}$ $M$ solution in 0.03 $M$ acetic acid decreased to 1.50 × $10^{-4}$ in 44 hours. In a 0.0167 $M$ solution of N-methylpyrrole and 0.03 $M$ acetic acid, the concentration decreased to 0.30 × $10^{-4}$. An approximate rate constant is 2 × $10^{-4}$.

**Synthesis of 3,5,4′-Tricarbethoxy-4,5′-dimethyl-3′-hydroxydipyrrylmethene (VIII).**—3-Hydroxy-4-carbethoxy-5-methylpyrrole (suspension of 0.50 g. in 50 cc. of ethanol) was slowly added, with shaking, to a solution of 2-formyl-3,5-dicarbethoxy-4-methylpyrrole (0.76 g. in 100 cc. of ethanol containing 1.0 cc. of concd. HCl). The solution turned yellow rapidly, and the 3-hydroxy-4-carbethoxy-5-methylpyrrole went into solution. After several hours at 0°, yellow needles formed; yield, after one crystallization from ethanol, was 0.70 g. The product, after three crystallizations from ethanol, melted at 237–240° dec. Beilstein test for halogen is negative. *Anal.* Calcd. for $C_{20}H_{24}O_7N_2$: C, 59.40; H, 5.98. Found: C, 59.53; H, 5.90. It shows (in alcohol) absorption bands with $\lambda_{\max}$ 3700 and 4430 Å. and $\epsilon$ 1.47 and 1.43 × $10^4$. The compound is the free base, which precipitated from HCl solution, showing it to be a very weak base.

**Synthesis of 1,4,5′-Trimethyl-3,5,4′-tricarbethoxy-3′-hydroxydipyrrylmethene (XIV).**—This was prepared from 0.30 g. of 3-hydroxy-4-carbethoxy-5-methylpyrrole and 0.50 g. of 2-formyl-3,5-dicarbethoxy-1,4-dimethylpyrrole in a manner similar to that described above. The product was precipitated by slow addition of water, and recrystallized from ethanol; yield 0.60 g. After three crystallizations from ethanol, the product was long yellow needles melting at 214–216° dec., $\lambda_{\max}$ 3980 Å. and $\epsilon$ 1.23 × $10^4$. A Beilstein test for halogen was negative, showing the product to be the free base. *Anal.* Calcd. for $C_{21}H_{26}O_7N_2$: C, 60.28; H, 6.27. Found: C, 60.13; H, 6.17.

**Synthesis of 1,3,5,5′-Tetramethyl-4,4′-dicarbethoxy-3′-hydroxydipyrrylmethene (XV).**—To a solution of 2-formyl-1,3,5-trimethyl-4-carbethoxypyrrole (0.9 g. in 100 cc. of ethanol containing 1.0 cc. of concd. HCl) was added a sus-

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[13] At high concn. of acetic acid (higher than used in the majority of experiments) there appeared to be a slight effect on the absorption maximum.

[14] A. H. Corwin and W. M. Quattlebaum, THIS JOURNAL, **58**, 1081 (1936).

[15] E. Benary and B. Silbermann, *Ber.*, **46**, 1366 (1913).

pension of 3-hydroxy-4-carbethoxy-5-methylpyrrole (0.7 g. in 50 cc. of ethanol). The hydroxypyrrole went into solution, which turned orange, then deep red. After 15 minutes it was neutralized with aqueous sodium bicarbonate and allowed to stand overnight in the ice-box. The crude product (1.2 g.) was crystallized twice as orange plates from hexane and benzene; m.p. 214–216° dec., $\lambda_{max}$ 4150 Å., and $\epsilon$ 1.72 × $10^4$. When crystallized very slowly, yellow needles were obtained. This product had $\lambda_{max}$ 4150 Å. and $\epsilon$ 1.78 × $10^4$. *Anal.* Calcd. for $C_{19}H_{24}O_5N_2$: C, 63.32; H, 6.71. Found: orange plates, C, 63.31; H, 6.88; yellow needles, C, 63.50; H, 6.90. This N-methyldipyrrylmethene thus appears to have two crystal forms.

**Condensation of 3,5,4'-Tricarbethoxy-4,3',5'-trimethyldipyrrylmethene with 3-Hydroxy-4-carbethoxy-5-methylpyrrole.**—The dipyrrylmethene (0.50 g.) and $\alpha$-free pyrrole (0.21 g.) were added to 25 cc. of purified dioxane. The addition of a pinch of powdered $KHSO_4$, with shaking, caused the color to change from red to yellow almost instantly. In 15 minutes, 25 cc. of water was added slowly to precipitate the product, which, after drying, melted over a wide range in the vicinity of 140°. The presence of about 10% 3,5,4'-tricarbethoxy-4,5'-dimethyl-3'-hydroxydipyrrylmethene (VIII) was indicated by the absorption spectra, which showed two bands of about equal intensities at *ca.* 3700 and 4430 Å. A drop of *N* HCl in the absorption cell caused almost quantitative cleavage to VIII over a period of several hours. This dipyrrylmethene presumably is formed by the cleavage of a tripyrrylmethane intermediate X, which has not been analyzed because of purification difficulties.

**Attempted Condensation of 3,5,4'-Tricarbethoxy-4,5'-dimethyl-3'-hydroxydipyrrylmethene (VIII) with 3,5-Dimethyl-4-carbethoxypyrrole (VI).**—A solution which was 0.001 and 0.02 *M*, respectively, with respect to VIII and VI showed no decrease in light absorption at 4430 or 3700 A. in 40 hours at room temperature.

**3,5,4'-Tricarbethoxy-4,3',5'-trimethyldipyrrylmethene (III).**—The hydrochloride was prepared by the method of Corwin and Quattlebaum.[14] The free base[3b] was prepared by shaking the hydrochloride with a suspension of calcium hydroxide in benzene, filtering, precipitating in hexane and recrystallizing twice from hexane–benzene, and from anhydrous acetone.

**3,5,4'-Trimethyl-4,3'-dicarbethoxy-5'-chlorodipyrrylmethene (I).**—The hydrochloride was prepared in 45% yield by the method of Fischer, Sturm and Friedrich,[16] except that benzene was used as solvent. The free base was prepared as described above, and recrystallized twice from acetone; m.p. 145–146°.

**3,5,4'-Trimethyl-4,3'-dicarbethoxy-5'-bromodipyrrylmethene (II).**—The hydrobromide was prepared by the method of Corwin and Viohl.[17] The free base was prepared as above and recrystallized twice from a 2:1 mixture of acetone and hexane.

**3,5,3'-Trimethyl-4,4'-dicarbethoxy-5'-bromodipyrrylmethene (V).**—This was also prepared by the method of Corwin and Viohl.[17]

**3,4,3',5'-Tetramethyl-4,4'-dicarbethoxydipyrrylmethene (IV).**—This was prepared by the method of Piloty, Krannich and Will.[18] The free base[3a] was prepared as above and was recrystallized twice from hexane–benzene, and from acetone.

**Synthesis of 3,5,4',3'',5''-Pentamethyl-4,3',4''-tricarbethoxy-5'-chloro-2,2',2''-tripyrrylmethane.**—3,5,4'-Trimethyl-4,3'-dicarbethoxy-5'-chlorodipyrrylmethene (0.30 g.) and an equivalent amount of 3,5-dimethyl-4-carbethoxypyrrole are dissolved in 25 cc. of absolute ethanol containing one drop lactic acid. The methane precipitated overnight in the ice-box. It was filtered, washed with ether and recrystallized from absolute methanol by very slowly cooling with Dry Ice; yield 0.30 g., m.p. 231–232° dec.

*Anal.* Calcd. for $C_{27}H_{34}O_6N_3Cl$: C, 60.98; H, 6.61. Found: C, 60.92; H, 6.45.

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(16) H. Fischer, E. Sturm and H. Friedrich, *Ann.*, **461**, 267 (1928).

(17) A. H. Corwin and P. Viohl, THIS JOURNAL, **66**, 1137 (1944).

(18) O. Piloty, W. Krannich and H. Will, *Ber.*, **47**, 2544 (1914).

BALTIMORE, MARYLAND

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

# Rauwolfia Alkaloids. XIV. Derivatives of Yohimbé Alkaloids

BY CHARLES F. HUEBNER, R. LUCAS, H. B. MACPHILLAMY AND HYLA AMES TROXELL

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A series of esters of yohimbine, corynanthine and $\alpha$-yohimbine have been prepared for pharmacological testing as reserpine substitutes. The amide of yohimbic acid was obtained by the action of sodium amide on yohimbine in liquid ammonia. The synthesis of N-methylyohimbine and yohimbhydrazide is reported.

Reserpine, a sedative and hypotensive alkaloid from *Rauwolfia serpentina Benth,* has been shown to be an ester of 3,4,5-trimethoxybenzoic acid. Since methyl reserpate, the alcoholic portion of this ester, has been postulated to have the pentacyclic ring system found in the yohimbé alkaloids,[1] and since methyl reserpate does not show the characteristic physiological activity of reserpine, it seemed pertinent to prepare esters of certain of the yohimbé alkaloids. Yohimbine and two of its stereoisomers, corynanthine and $\alpha$-yohimbine,[2] were included in this study. In addition some new derivatives of yohimbine, involving transformations of the carbomethoxyl and imino functions, have been synthesized.

Esterification of these hydroxyl-bearing alkaloids was accomplished by reaction with excess acid chloride in pyridine at room temperature. O-Benzoyl, -anisoyl, -veratroyl, and -3,4,5-trimethoxybenzoylyohimbine, O-3,4,5-trimethoxybenzoylcorynanthine and O-3,4,5-trimethoxybenzoyl-$\alpha$-yohimbine were prepared by this method. With acetic anhydride as the acylating agent, yohimbine gave crystalline O-acetylyohimbine of m.p. 215–220°. Schomer[3] has described what is presumably this compound as an amorphous material of m.p. 133°. That O- rather than N-acylation has occurred, is demonstrated by the typical indole ultraviolet absorption spectra of the products. Janot and Goutarel[4] have shown that N-acetylation, as exemplified by O,N-diacetylyohimbine, shifts the shortest of the two characteristic indole maxima

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(1) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. André, *Helv. Chim. Acta*, **37**, 59 (1954).

(2) Our sample of $\alpha$-yohimbine was isolated from *Rauwolfia Canesens* L. The alkaloid obtained from this source previously has been known as "rauwolscine" until its recent identification as $\alpha$-yohimbine by A. Chatterjee, A. Bose and S. Pakrashi, *Chem. and Ind.*, 491 (1954).

(3) (a) A. Schomer, *Arch. d. Pharm.*, **265**, 509 (1927); (b) M. M. Janot and R. Goutarel, *Bull. soc. chim.*, [5] **10**, 383 (1943).

(4) (a) M. M. Janot and R. Goutarel, *Compt. rend.*, **229**, 360 (1949); (b) M. M. Janot and R. Goutarel, *Ann. pharm. franc.*, **1**, 552 (1949).