Experimental

Trithioacetophenone.—This compound was used as a source of thioacetophenone. It dissociates to the monomer above its melting point. Trithioacetophenone was prepared by the method described by Baumann and Fromm.[7] The product was readily recrystallized from a mixture of equal volumes of alcohol and acetone, yielding hexagonal bars, m. p. 121–122.1° cor. The yield was 21 g., or 37%.

Anal. Calcd. for $C_{24}H_{24}S_3$: C, 70.58; H, 5.88; S, 23.53. Found: C, 70.49; H, 5.97; S, 23.31.

Raney Nickel.—The Raney nickel was prepared in the usual way[8] and stored under absolute alcohol. When needed it was shaken up, and a portion of the alcohol suspension transferred to a 50-ml. centrifuge tube and centrifuged. The alcohol was decanted, and 20 ml. of dry xylene was added. The nickel was again shaken up, and the suspension centrifuged. The washing with dry xylene was repeated 5 or 6 times to remove alcohol, and the nickel was then used as a xylene suspension.

α,α'-Dimethylstilbene.—Fifty ml. of this xylene suspension containing approximately 8 g. of Raney nickel (4 times the calculated quantity) was placed in a small flask, and 4 g. of trithioacetophenone added. The mixture was heated in an atmosphere of nitrogen at 145–150° on an oil-bath for ninety minutes. After cooling, the residue was removed by filtering through a sintered glass plate. Hydrogen sulfide was evolved when this nickel residue was treated with hydrochloric acid, indicating the presence of nickel sulfide. The clear xylene solution was distilled under vacuum to remove most of the xylene, and the residual brown oil (about 5 ml.) was stored overnight in the refrigerator. Flat colorless plates of a sulfur-free compound were deposited. These were filtered, washed with cold petroleum ether and dried. They melted at 105–106° cor. The *trans* form of α,α'-dimethylstilbene is reported to melt at 107°, while the *cis* form melts at 67°.[9] A second crop of crystals was recovered by the addition of alcohol to the mother liquor. The total yield was 0.55 g., or 18%.

Anal. Calcd. for $C_{16}H_{16}$: C, 92.3; H, 7.7. Found: C, 92.06; H, 7.68.

In cold carbon tetrachloride this compound forms a dibromide which can be recrystallized from methanol in white needles, m. p. 152.5–153° cor., corresponding to the dibromide reported by Levy.[10]

Anal. Calcd. for $C_{16}H_{16}Br_2$: C, 52.2; H, 4.3. Found: C, 51.9; H, 3.8.

Attempted Condensation with Copper Powder.—Copper powder was used in the place of Raney nickel in one experiment. Approximately 7 g. of freshly reduced copper powder (4 times the calculated quantity) were refluxed in xylene with 4 g. of trithioacetophenone. The mixture was stirred vigorously. After three hours the copper was not markedly discolored. After six hours, refluxing and stirring were stopped. The mixture was cooled and filtered. The copper residue contained some sulfur. Approximately 50% of the trithioacetophenone was recovered unchanged when the xylene solution was concentrated. The mother liquor yielded a small amount of an intractable, sulfur-containing oil.

Summary

trans-α,α'-Dimethylstilbene has been prepared by the reaction of thioacetophenone with Raney nickel.

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[7] Baumann and Fromm, *Ber.*, **28**, 895 (1895).

[8] "Organic Syntheses," **21**, 15 (1941).

[9] Von Wassely and Wellaba, *Ber.*, **74B**, 777 (1941).

[10] Levy, *Bull. soc. chim.*, **29**, 878 (1921).

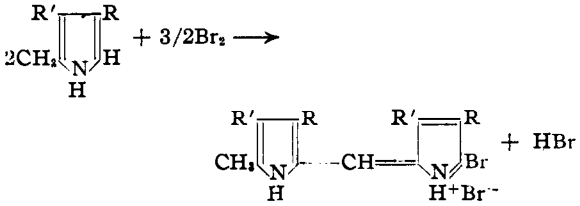
BLOOMINGTON, INDIANA RECEIVED MARCH 24, 1944

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

The Condensation of Pyrroles with Bromine. A Self-Oxidation and a New Type of Displacement Reaction[1,2]

BY ALSOPH H. CORWIN AND PAUL VIOHL[3]

One of the reactions exploited frequently by Hans Fischer and his collaborators in the synthetic proofs of the structures of porphyrin derivatives is the unorthodox condensation of α-free-α'-methyl pyrroles by means of bromine. This condensation generally gives 5-bromo-5'-methyldipyrrylmethene hydrobromides in yields of about 50%.



Reactions of this type have no analogy outside the field of pyrrole chemistry and their course is not thoroughly understood. Fischer and Scheyer[4] have shown that in one case this condensation led mainly to a product of unknown constitution.[5] Fischer and Bäumler[6a] cite another example of the more or less unpredictable course of the condensation[7] and also present a surprising case in which the substitution of an ethyl group in the β-position completely blocks the reaction. All the foregoing facts prompt an inquiry into the mechanism of the condensation and its impor-

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[1] Studies in the Pyrrole Series. XII; Paper XI, Brunings and Corwin, THIS JOURNAL, **66**, 337 (1944).

[2] This paper is from the doctoral dissertation of Paul Viohl, The Johns Hopkins University, 1939. A part of it was presented at the Baltimore Meeting of the American Chemical Society, April, 1939. Original manuscript received November 17, 1943.

[3] Present address, U. S. Rubber Co., Detroit, Mich.

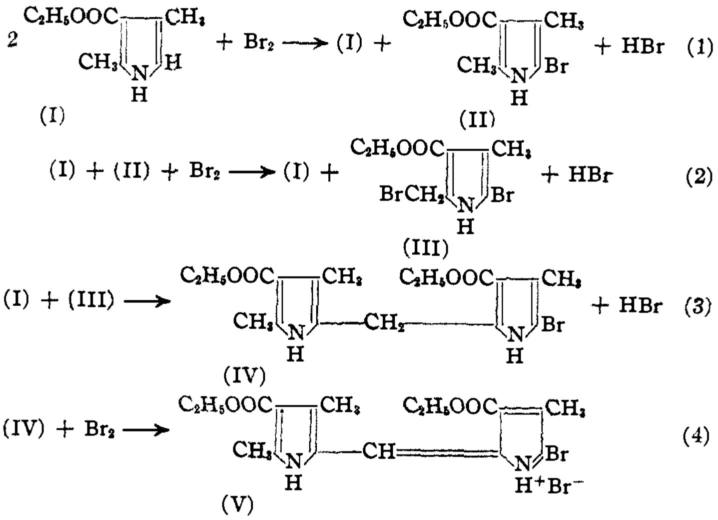
[4] Fischer and Scheyer, *Ann.*, **434**, 242 (1923).

[5] This article undoubtedly contains an accidental error since the tentative structural formula advanced on p. 242 corresponds to a hydrobromide with the empirical formula $C_{14}H_{13}ON_2Br_6$ while the empirical formula calculated for the analytical data on p. 251 is $C_{14}H_{15}ON_2Br_6$.

[6] Fischer and Bäumler, *ibid.*, **468**, (a) 60, (b) 73, (c) 63 (1929).

[7] Curiously enough, this paper contains the converse error to that mentioned in note 5. The tentative structural formula advanced on p. 60 corresponds to the empirical formula $C_{16}H_{19}ON_2Br_5$ while the empirical formula calculated for analysis on p. 72 is $C_{16}H_{17}ON_2Br_5$.

CHART I



tance in structural determinations makes it desirable to learn whether still further limitations upon its reliability exist. For this purpose we have chosen to study the bromination of 2,4-dimethyl-3-carbethoxy pyrrole (I) to 3,5,4′-trimethyl-4,3′-dicarbethoxy-5′-bromo dipyrrylmethene hydrobromide (V).

The condensation by bromine has been postulated by Fischer[8] to consist of four steps as shown in Chart I.

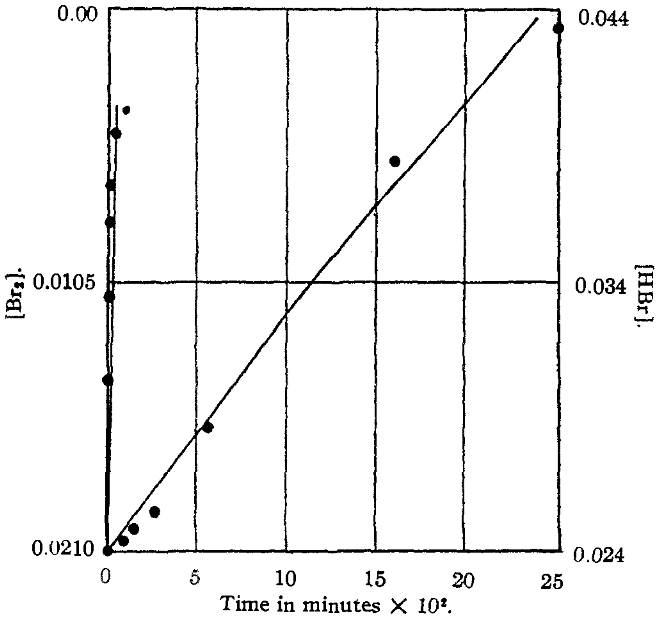


Fig. 1.—Decrease in $[Br_2]$ and increase in [HBr] in a 0.02 molar solution of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole at 15°.

Fischer's assumption that compound II reacts with bromine faster than compound I (Reaction 2) is surprising. We have demonstrated experimentally that the opposite is true. By stopping the reaction after the addition of one mole of bromine, the α-bromopyrrole II can be isolated in good yields.[6b] This experiment makes the assumption of reaction 3 untenable. This conclusion may be further substantiated by the use of compound II as the starting material in the preparation of the methene. Under these conditions, which exclude the presence of compound I, methene V is formed in appreciably better yield than when compound I is used as the starting material.

Our experiments, cited below, make it probable that the sequence of reactions in the formation of the methene can best be represented by Chart II.

CHART II

$$(I) + Br_2 \longrightarrow (II) + HBr \qquad (5)$$

$$2\,(II) + 1Br_2 \longrightarrow 1\,(II) + (III) + HBr \qquad (6)$$

$$(II) + (III) \longrightarrow (V) \qquad (7)$$

At the end of reaction 5 compound II exists in solution in the presence of unreacted bromine and hydrogen bromide. Experiment shows that bromopyrrole II is unstable in the presence of either of these reagents. Hydrogen bromide catalyzes a reaction which causes the liberation of further quantities of hydrogen bromide. Bromine is consumed by the pyrrole derivative. The relative rates of these two reactions are plotted in Fig. 1, in which the nearly vertical line represents the rate of disappearance of bromine and the oblique line represents the rate of liberation of hydrogen bromide in the absence of bromine.

The reaction of compound II with bromine is roughly a thousand times as fast as the reaction catalyzed by hydrogen bromide. This demonstrates that the second step in the bromination reaction involves the consumption of bromine.

There are analogies in the literature[9] for several modes of bromination of the α-bromopyrrole II in addition to the formation of compound III from it. Since compound III is the most orthodox product, however, it should be examined as a possible intermediate in the reaction. No attempts to prepare it have met with success. We were, consequently, forced to resort to an indirect method to find whether or not it could be an intermediate in the reaction. This consisted in establishing an analogy for reaction 7.

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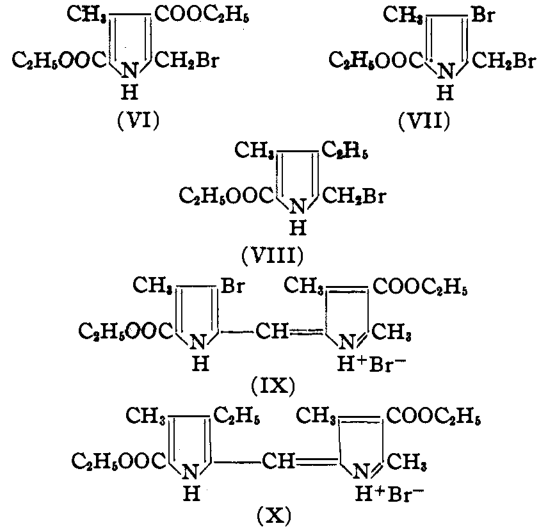
(8) Fischer and Orth, "Die Chemie des Pyrrols," Bd. II, 1 Hälfte, Akad. Verlag., Leipzig, 1940.

(9) The analogies of the perhalophenols and naphthols may be cited. See, for example, Zincke and Schaum, *Ber.*, **27**, 539 (1894); Biltz, *ibid.*, **37**, 4005 (1904); Zincke and Broeg, *Ann.*, **363**, 228 (1908); Thiele and Eichwede, *Ber.*, **33**, 673 (1900).

Although Fischer and Bäumler[6c] once proposed reaction 7 as an explanation for the formation of α-methyl-α′-bromomethenes, such a condensation has never been carried out with well-characterized substances. We have attempted three analogous condensations, the reactions of α-bromopyrrole II with compounds VI, VII and VIII, Chart III.

CHART III



Compound VI does not react with pyrrole II. Compounds VII and VIII do undergo condensation yielding methenes IX and X, respectively. Methene X was identified as the free base, prepared by the method of Fischer, Berg and Schormüller.[10] These reactions constitute a new method for preparing dipyrrylmethenes in addition to furnishing analogies for the postulated reaction 7 leading to methene V. The fact that pyrrole VI does not react shows that the new synthesis is not perfectly general and suggests that other pyrrylmethyl bromides with electron-attracting substituents may not undergo the reaction. What the limitations may be upon the nuclear-brominated pyrrole remains for further experiments to determine.

If reaction 7 were the last step in the formation of methene V, the condensation should interrupt the bromination (reaction 6) after the consumption of half a mole of bromine. This was tested by studying the rate of disappearance of bromine in a solution of compound II. The results are plotted in Fig. 2.

In Fig. 3 the same data are plotted as the reciprocal of the bromine concentration against the time. This should be linear if the reaction were bimolecular. The arrow marks the point at which one-half mole of bromine has been consumed.

The curve of Fig. 3 shows greater deviation from the bimolecular relationship beyond the half-way point than before it. In spite of the change in the velocity of the bromination after half a mole has reacted, bromination does not entirely cease at this point. This is not necessarily inconsistent with the postulation of reaction 7 as the final condensation in the series, provided that the final product is not isolated in stoichiometric proportions. We have been unable, up to this time, to obtain yields greater than 75% of the theoretical amount of compound V. In addition, successive increments of bromine beyond the theoretical amount all give yields of the methene between 65 and 75%. The remaining material, if reaction 6 truly represents

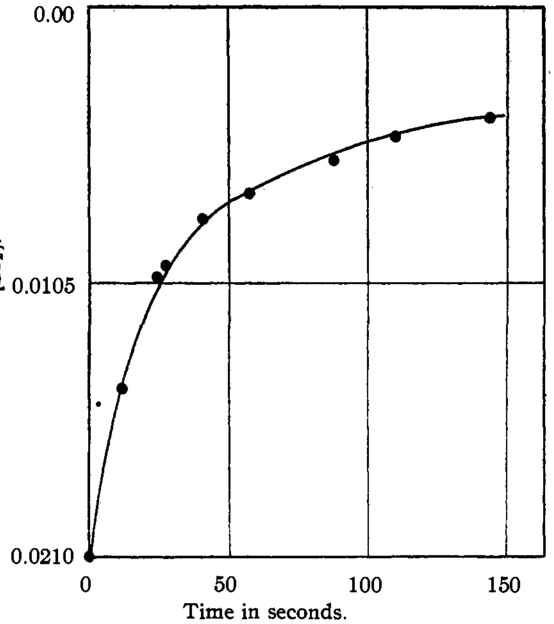


Fig. 2.—Decrease in [Br$_2$] in a 0.02 molar solution of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole at 15°.

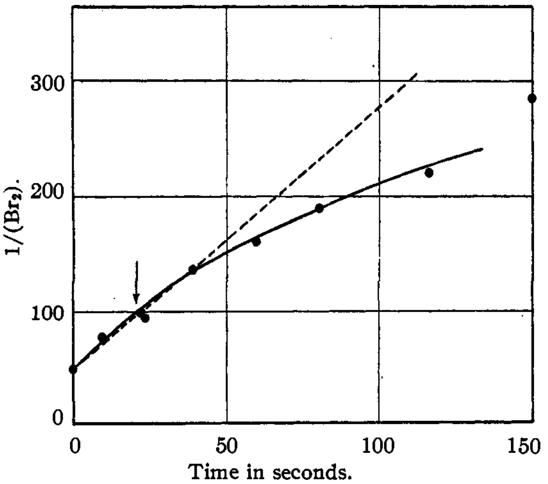


Fig. 3.—Reciprocal of bromine concn. *vs.* time in a solution 0.02 molar with respect to 2,4-dimethyl-3-carbethoxy-5-bromopyrrole and 0.021 molar with respect to bromine.

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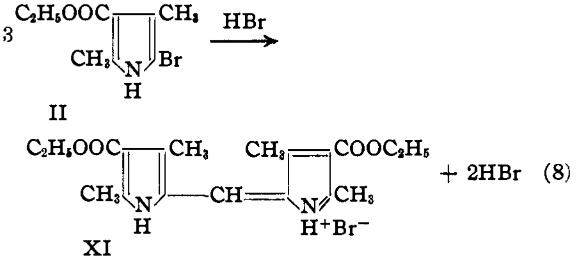
(10) Fischer, Berg, and Schormüller, *Ann.*, **480**, 129 (1930).

the course of the bromination, should be the unknown methene obtained by brominating compound V in the α-methyl group. All attempts to isolate this substance have been unsuccessful so far. Fischer[11] has recorded the isolation of similar α-bromomethyl-α′-bromomethenes. The difficulty of brominating methene V as contrasted to the ease of bromination of pyrrole II indicates that these dibrominated methenes are probably formed by condensations similar to reaction 7 but involving two moles of dibrominated pyrrole (III). Thus the products of the bromination reaction with a given set of substituents will depend upon the outcome of the competition of bromine and dibrominated pyrrole for the α-bromopyrrole.

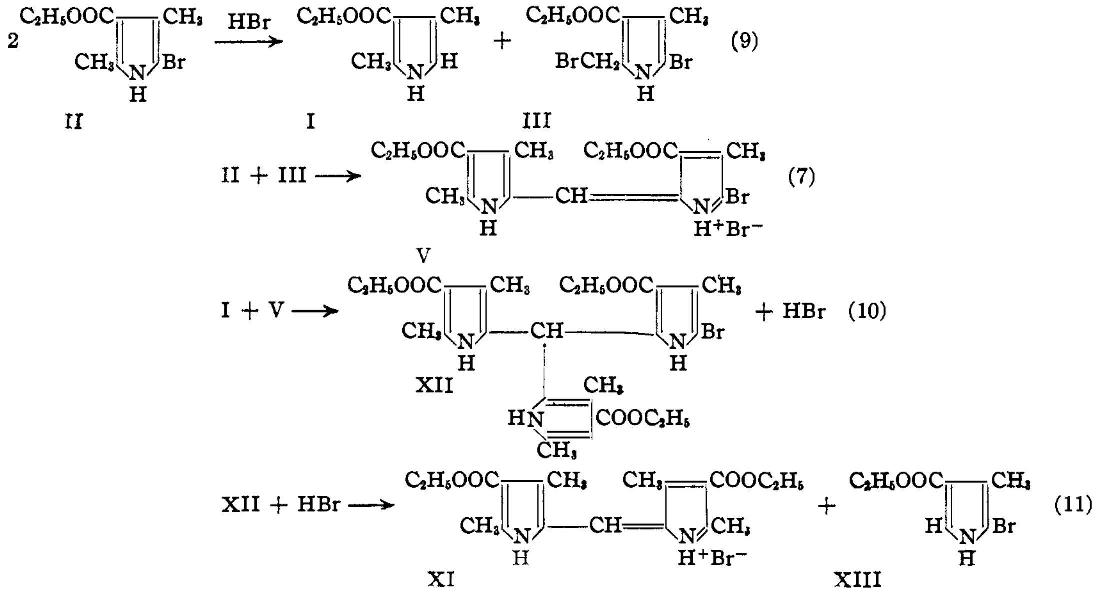
The experiments reported above establish the sequence of reactions in the formation of the particular bromomethene (V) formed from this set of starting materials. The study shows for the first time that a reaction catalyzed by hydrogen bromide is present to compete with the main reaction. Changes in substituents may alter the relative importance of these two reactions. For this reason the nature of the acid-catalyzed condensation was investigated. It was found that the reaction can be represented by equation 8.



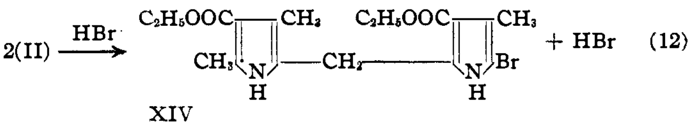
Methene XI, unlike the starting pyrrole II, contains no ring-bound halogen. The fact that the methene hydrobromide contains one more than twice the number of carbon atoms in the original pyrrole forces the conclusion that three molecules of pyrrole II are involved in the reaction and suggests the presence of a tripyrrylmethane intermediate. Such an intermediate would require two condensation steps. These can be arranged in at least two different sequences given in Schemes A and B of Chart IV.

CHART IV

Scheme A



Scheme B



$$(\mathrm{XIV}) + (\mathrm{II}) \xrightarrow{\mathrm{HBr}} (\mathrm{XII}) \qquad (13)$$

$$(\mathrm{XII}) + \mathrm{HBr} \longrightarrow (\mathrm{XI}) + (\mathrm{XIII}) \qquad (11)$$

In either scheme, to account for the yield of hydrogen bromide actually obtained, it is necessary to assume that pyrrole XIII is unstable and decomposes to give hydrogen bromide.

Our data do not permit us to choose between Schemes A and B. The following considerations are pertinent, however. Reaction (9) requires

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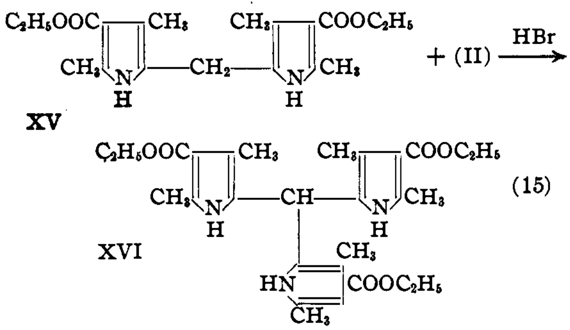
(11) Fischer, Baumann and Riedl, *Ann.*, **475**, 216 (1929).

bromopyrrole II to be an oxidizing agent, more specifically, a brominating agent. The oxidizing property of the pyrrole was confirmed experimentally. It was shown that the pyrrole II will oxidize iodide ion to free iodine in the presence of acetic acid according to the equation

$$(\text{II}) + \text{I}^- \xrightarrow{\text{H}^+} (\text{I}) + {}^1/_2\text{I}_2 + \text{Br}^- \qquad (14)$$

Thus the halogen atom in pyrrole II is of the type commonly referred to as a "positive halogen." The oxidation of a dipyrrylmethane was also accomplished in a reaction analogous to 13. 3,5,3',5'-tetramethyl-4,4'-dicarbethoxydipyrrylmethane (XV, Chart V) was treated with pyrrole II in the presence of hydrogen bromide. The corresponding methene (XI) was obtained in good yields. It is possible that tripyrrylmethane XVI is a transitory intermediate in this reaction.

CHART V



XV

XVI

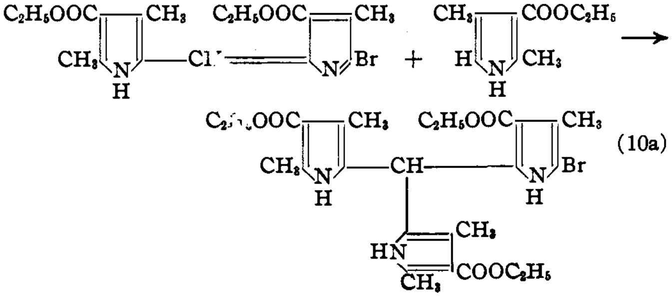
(15)

$$(\text{XVI}) + \text{HBr} \longrightarrow (\text{XI}) + (\text{I}) \qquad (16)$$

The success of this experiment shows that the second step (reaction 13) of Scheme B is a possible one.

Utilizing the tripyrrylmethane synthesis of Paden, Corwin and Bailey,[12c] tripyrrylmethane XII, a hypothetical intermediate in the self-oxidation of pyrrole II, reaction (10), has been synthesized (Chart VI)

CHART VI



(10a)

Reaction (10a) differs from reaction (10) only in the employment of the free base instead of the hydrobromide of methene V for the condensation.

An inspection of the formula of tripyrrylmethane XII shows that it might be capable of cleavage to give either of two dipyrrylmethenes, V or XI The reaction sequence of Chart III requires that it cleave to give methene XI. Experimentally, it can be made to yield either methene. Rapid cleavage with rapid precipitation of the product leads to methene V, while slow cleavage with slow precipitation of the product leads to methene XI. This difference can be achieved by taking advantage of the differences in solubility of the two methenes. Methene V is more soluble in organic solvents than is methene XI. In addition, the products of the reaction are both stable under the conditions of the reaction. As a result, when a relatively poor solvent is used, methene V is obtained in good yield from the reaction with hydrogen bromide. When a relatively good solvent is used, methene V remains in solution. Under these conditions, or under conditions where the rapid formation of a large mass of tripyrrylmethane XII is prevented, the reaction is displaced due presumably to the instability of bromopyrrole XIII. Methene XI is formed slowly, precipitating out of the solution as formed. These latter conditions are duplicated when the α-bromopyrrole II is treated with hydrogen bromide and their presence accounts for the formation of methene XI in the self-oxidation reaction. These unusual reactions constitute the first case recorded in which a tripyrrylmethane can cleave in the presence of hydrogen bromide alone to yield two different dipyrrylmethenes. They also provide experimental justification for the formulation of reaction 11 for the self-oxidation reaction in both Schemes A and B.

To recapitulate the evidence for Scheme A, we have established analogies for reactions 9 and 7 and have duplicated reactions 10 and 11. Hence we feel that this scheme has firm experimental justification.

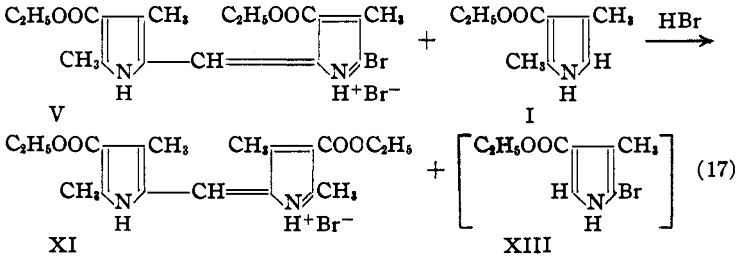
In Scheme B, we have no analogy for reaction 12, but we do have one for reaction 13 and reaction 11 has been verified. Our inability to present an analogy for reaction 12 does not necessarily invalidate Scheme B, but the more complete analogy for the reactions in Scheme A lead us to prefer it.

A study of the reactions of Charts V and VI leads to the prediction that conditions can be found for the conversion of methene V into methene XI. Actually, when methene V is dissolved at room temperature and treated with hydrogen bromide and pyrrole I, methene XI precipitates slowly but in good yield. This reaction is shown in Chart VII.

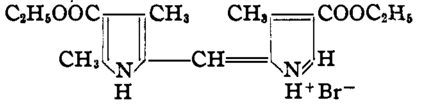
The discovery of this "displacement reaction," in which all of the structural elements involved are organic, points to the necessity for examining carefully the products obtained from reactions involving dipyrrylmethenes and similar pigments since it shows that conditions may exist under which they may be converted to pigments of different structure.

Because of the peculiarities developed above, the structure of methene V was reinvestigated.

CHART VII



Analysis and molecular weight determination have shown the molecular formula of the free base to be $C_{18}H_{21}O_4N_2Br$. The conversion of the methene to methene XI by the action of pyrrole I (Reaction 17) in yields greater than those corresponding to the amount of pyrrole I added makes it highly probable that the dimethylcarbethoxy substituted nucleus has the configuration assigned. The only remaining piece of evidence



XVII

required for a complete structural proof is an independent means for establishing the configuration of the halogen-containing pyrrole ring. For purposes of structural argument we may assume that the configuration of the β-substituents might be reversed in this methene, giving methene XVII.

Because of the difficulties in absolute identification of dipyrrylmethenes, it was decided that the comparisons between the two series would be made between tripyrrylmethanes, most of which possess reversible melting points. Two series of reactions were devised which would lead to identical products if the methene V had the structure XVII but which would lead to different products if formula V were correct. These reaction series are given in Chart VIII.

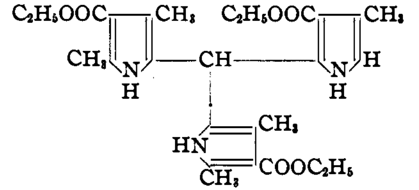
Comparison of tripyrrylmethanes XVIII and XXIII shows them to be different and thus shows that methene V does not have the configuration of methene XVII. Methene XVII was prepared by the bromination of methene XXII but, as expected, its base is not suitable for purposes of identification. It melts with decomposition at 151° whereas methene V (base) melts with decomposition at 153°.

The validity of this structural proof rests upon the correctness of the structure of aldehyde XXI. This was established by Fischer and Wiedemann[13a]

CHART VIII

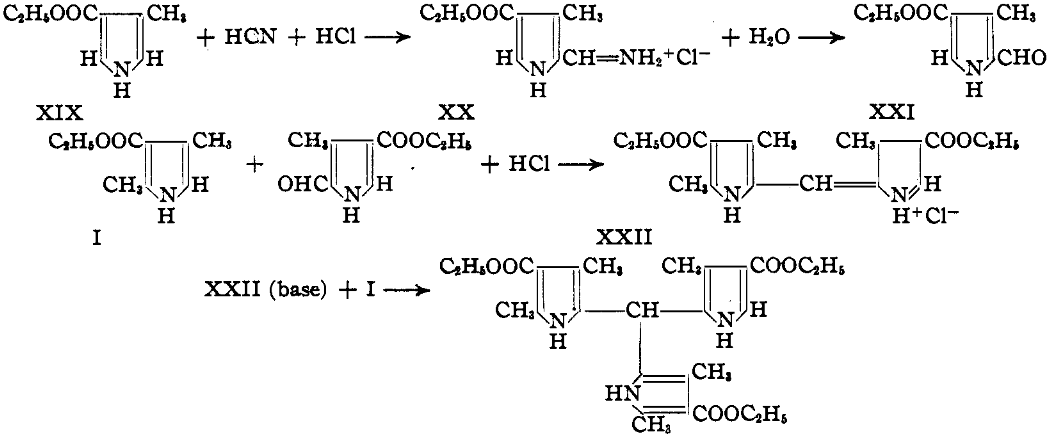
SERIES 1

Reaction 13, Chart V, followed by hydrogenation of XII with palladium on charcoal and magnesium oxide to give compound XVIII.[12a]



XVIII

SERIES 2



XXIII

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(12) Corwin, Bailey and Viohl, THIS JOURNAL, **64**, (a) 1267, (b) 1272 (1942); (c) Paden, Corwin and Bailey, *ibid.*, **62**, 418 (1940).

(13) Fischer and Wiedemann, *Z. physiol. Chem.*, **155**, (a) 52, (b) 58, (c) 59 (1926).

who converted it into 2,3-dimethylpyrrole by the Wolff–Kishner reaction.

The reactions formulated in Chart VIII thus lend strong substantiation to the correctness of the formulation of methene V.

One of the authors (P. V.) wishes to acknowledge a grant-in-aid from the Hynson, Westcott and Dunning Research Fund.

Experimental Part

2,4-Dimethyl-3-carbethoxy-5-bromopyrrole (II).[6b]—(a) Sixteen and seven-tenths grams of 2,4-dimethyl-3-carbethoxypyrrole (I) dissolved in 100 cc. of methanol was cooled to −60° and a solution of 16.8 g. of bromine in 25 cc. of methanol was added with shaking in five minutes. After ten minutes, the bromopyrrole was precipitated by pouring into 700 cc. of water containing 10 g. of sodium bicarbonate. The reaction flask was washed with two 10-cc. portions of methanol. The product was filtered off with suction and washed with water; yield, 16.5 g. or 67%. The product melted with decomposition at 97°. Two recrystallizations from alcohol–water raised the decomposition point to 110–112°.

(b) One and three-tenths grams of potassium hydroxide was dissolved in 10 cc. of methanol, cooled in an ice-bath and 1.68 g. of 2,4-dimethyl-3-carbethoxypyrrole dissolved in the mixture. A solution of 1.6 g. of bromine in 3.2 cc. of methanol was added, keeping the temperature below 10°. Potassium bromide separated. After stirring, the mixture was poured into 100 cc. of cold water. The pyrrole separated and was filtered off. It was recrystallized from carbon tetrachloride containing a drop of pyridine.

Preparation (a) is more satisfactory than (b). The decomposition point of this compound does not serve as a test for its purity. The decomposition of adhering crystals on the sides of the melting point tube catalyzes the decomposition of the bulk of the material. The critical impurity is acid. Samples containing more organic impurity and less acid decompose at a higher temperature than samples containing less organic impurity but having a trace of acid.

Anal. Calcd. for $C_9H_{12}O_2NBr$: C, 43.92; H, 4.92. Found: C, 43.64, 43.93; H, 4.93, 4.95.

3,5,4′-Trimethyl-4,3′-dicarbethoxy-5′-bromodipyrrylmethene Hydrobromide (V).—(a) **From 2,4-Dimethyl-3-carbethoxypyrrole.**—Sixteen and seven-tenths grams of 2,4-dimethyl-3-carbethoxypyrrole was dissolved in 300 cc. of ether, cooled to −5° and a solution of 32.0 g. of bromine in 60 cc. of glacial acetic acid was added with stirring during forty-five minutes. The temperature was kept below 0°. The flask was allowed to stand in an ice-box for ninteen hours. The red solid was filtered off and washed with 120 cc. of ether; yield 17.2 g. or 70%.

The free base was prepared by finely pulverizing the methene hydrobromide in a mortar and grinding with dilute ammonia solution until the red paste had a definite odor of ammonia. The solid was filtered off and washed with water. Repeated hot hexane extracts were made. The first few extracts were bad but the methene free base crystallized out of the later ones in beautiful rosets melting with decomposition at 153°.

Anal. Calcd. for $C_{18}H_{21}O_4N_2Br$: C, 52.82; H, 5.17; mol. wt., 409. Found: C, 52.89; H, 5.17; mol. wt. (ebullioscopic in chloroform), 462, 420.

(b) **From 2,4-Dimethyl-3-carbethoxy-5-bromopyrrole (II).**—Seven and six hundredths grams of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole was dissolved in 60 cc. of glacial acetic acid, cooled to 10–15° and a solution of 4.59 g. of bromine in 25 cc. of glacial acetic acid was added with vigorous stirring during one hour. The temperature was maintained at 10–15°. After another hour, the precipitated methene hydrobromide was filtered off and washed with 50 cc. of ether; yield, 5.3 g. or 75.3%.

Similar preparations were made using one-half, three-fourths, and one mole of bromine per mole of bromopyrrole. The yields were 65.4, 72.6 and 75.3%, respectively. The preparation described under (b) yields a much more satisfactory product than that under (a).

The Rate of Disappearance of Bromine in a Solution of 2,4-Dimethyl-3-carbethoxy-5-bromopyrrole.—Two hundred fifty cubic centimeters of a 0.04 molar solution of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole in acetic acid and 250 cc. of an approximately 0.04 molar solution of bromine in acetic acid were prepared in separate flasks and placed in a 15° thermostat, 5 cc. of the bromine solution was pipetted into 50 cc. of approximately 0.1 *M* potassium iodide solution and the liberated iodine titrated with 0.0181 *N* sodium thiosulfate solution using starch as an indicator. This gave the initial bromine concentration.

Aliquots of 25 cc. each were pipetted out of each vessel and placed in two smaller Erlenmeyer flasks which were allowed to remain in the thermostat. The two aliquots were mixed and after ten seconds were poured into 150 cc. of approximately 0.05 *M* potassium iodide solution and crushed ice. The liberated iodine was titrated immediately with 0.0181 *N* sodium thiosulfate solution. Neither iodide ion nor iodine reacts with 2,4-dimethyl-3-carbethoxy-5-bromopyrrole rapidly at 0° under the conditions of the titration. A rapid titration is necessary to obtain reliable results. The blue color reappears on standing. Several measurements of this type were made at different time intervals. The table illustrates the results:

Time, sec.	Cc. of 0.0181 *N* $Na_2S_2O_3$ soln. per 25 cc. Br_2 soln.	Br_2 (after mixing)
0	116.0	0.021
10	75–76	.0137
23	56–57	.0102
24	56–57	.0102
40	42–43	.0077
60	36–37	.0066
90	30–31	.0055
120	25–26	.0046
150	19–20	.0035

The Rate of Disappearance of Bromine in a Solution of 2,4-Dimethyl-3-carbethoxypyrrole.—The solutions were prepared and the manipulations performed as described in the preceding experiment, except that 2,4-dimethyl-3-carbethoxypyrrole was substituted for the bromopyrrole there employed. The two 25-cc. aliquots were mixed and after six seconds (it was not practicable to get an earlier measurement) were poured into 150 cc. of approximately 0.05 molar potassium iodide solution and crushed ice. The liberated iodine was back titrated as described above. The following table gives the results.

Time, sec.	Cc. of 0.0181 *N* $Na_2S_2O_3$ soln. per 25 cc. Br_2 soln.	Br_2 (after mixing)
0	118.0	0.0213
6	3.0	.00054
8	1.0	.00018
8	1.1	.00020
12	0.3	.000054

From the results of this experiment, it is clear that the reaction proceeds so rapidly that it is impossible to make kinetic studies by the usual methods.

The Rate of Increase in the Hydrogen Bromide Concentration in the Self-Oxidation of Pyrrole II to Give Methene XI.—Two and forty-six hundredths grams (0.01 mole) of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole was dissolved in 477 cc. of dry diethyl ether and placed in a 15° thermostat, 22.8 cc. of a solution of hydrogen bromide in diethyl ether (0.44 *M*) was added and thoroughly mixed; 50-cc. aliquots were taken out at various time intervals and poured into 50 cc. of standard sodium hydroxide solution (0.0625 *M*) in a 250-cc. separatory funnel. After shaking, the layers were separated and the ether washed twice with 25-cc. portions of distilled water. The excess alkali and the washings were back titrated with standard hydrochloric acid solution (0.0616 *M*). The table illustrates the results:

Time, min.	Cc. HCl	Cc. NaOH to neutralize HBr	Moles HBr
0	31.24	19.2	0.0240
68	30.6	19.8	.0247
131	29.9	20.5	.0256
262	29.2	21.2	.0265
535	27.1	23.3	.0291
1590	19.23	31.1	.0388
∞	15.6	34.6	.0432

Reaction of 2,4-Dimethyl-3-carbethoxy-5-bromopyrrole with α-Bromomethylpyrroles. (a) **3,5,4′-Trimethyl-4,5′-dicarbethoxy-3-ethyldipyrrylmethene Hydrobromide**[10] **(X)**.—One and thirty-seven hundredths grams of 2-bromomethyl-3-ethyl-4-methyl-4-carbethoxypyrrole[14a] (VIII) and 1.23 g. of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole were dissolved in 15 cc. of carbon tetrachloride and warmed to 50°. Hydrogen bromide was liberated and an intense red color developed. After standing for one hour at room temperature and one hour in an ice-box, the precipitated methene hydrobromide was filtered off and washed with hexane; yield, 1.62 g. or 74%. The free base was prepared by grinding with dilute ammonia solution. Recrystallization from a small amount of hexane gave red needles melting at 90°. Mixed melting point with base prepared by the method of Fischer, Berg and Schormüller,[10] 90°.

(b) **2,5,4′-Trimethyl-4,5′-dicarbethoxy-3′-bromodipyrrylmethene Hydrobromide (IX)**.—Eight hundred and twelve milligrams (0.0025 mole) of 2-bromomethyl-3-bromo-4-methyl-5-carbethoxypyrrole[14b] was suspended in 20 cc. of glacial acetic acid, warmed to 40° and 0.676 g. (0.00275 mole) of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole was added in small portions over a period of about twenty minutes. Care was taken to see that the reaction went to completion since the presence of small quantities of starting material made it difficult to purify the free base of the methene. Dilution with about 20 cc. of ether and scratching caused the precipitation of the product which was allowed to stand in an ice-box for two hours and filtered off under nitrogen. Washing with ether gave a clean product; yield, 0.520 g. or 51%.

The free base was prepared by grinding with dilute ammonia solution. Several recrystallizations from hexane gave a pure product melting with decomposition at 135–136°.

Anal. Calcd. for $C_{18}H_{21}O_4N_2Br$: C, 52.82; H, 5.17. Found: C, 53.01; H, 5.19.

Attempts to perform this reaction with 2-bromomethyl-3,5-dicarbethoxy-4-methylpyrrole and 2,4-dimethyl-3-carbethoxy-5-bromopyrrole were unsuccessful.

Condensation of 2,4-Dimethyl-3-carbethoxy-5-bromopyrrole to 3,5,3′,5′-Tetramethyl-4,4′-dicarbethoxydipyrrylmethene Hydrobromide (XI).—Two and seventeen hundredths grams of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole was dissolved in 75 cc. of ether (distilled from sodium) in a 125-cc. Erlenmeyer flask equipped with a ground-glass stopper through which an inlet tube, leading to the bottom of the flask, and an outlet tube passed. The solution was cooled to 0° and oxygen-free nitrogen passed through the apparatus for ten minutes. After this, dry gaseous hydrogen bromide was bubbled through for fifteen seconds. The reaction mixture was allowed to warm up to room temperature and was kept in the dark for six hours. The red solid was filtered off and washed with ether; yield 0.95 g. or 76.5%. Attempts to isolate pyrroles from the filtrate failed. By increasing the concentration of the pyrrole and allowing the flask to stand overnight, the yield was increased to 95–100% of the theoretical value, based on the formation of one mole of methene from three of bromopyrrole.

The free base was prepared as usual and the dried product recrystallized from hexane. It melted with decomposition at 185°. Recrystallization from acetone gave red needles decomposing at 190°. Catalytic hydrogenation of the product gave a compound melting with slight decomposition at 230°. A mixed melting point with synthetic methane XV showed no depression.

Oxidation of Iodide Ion by 2,4-Dimethyl-3-carbethoxy-5-bromopyrrole.—A solution of potassium iodide in methanol was acidified with hydrobromic acid and bromopyrrole II was added. The liberation of iodine was instantaneous. Alternatively, a solution of potassium iodide was prepared in glacial acetic acid and treated with the bromopyrrole. The reaction was again instantaneous.

Oxidation of 3,5,3′,5′-Tetramethyl-4,4′-dicarbethoxydipyrrylmethane (XV) by 2,4-Dimethyl-3-carbethoxy-5-bromopyrrole.—Six hundred ninety milligrams of 3,5,3′,5′-tetramethyl-4,4′-dicarbethoxydipyrrylmethane and 1 cc. of 48% hydrobromic acid solution were dissolved in 50 cc. of dioxane (distilled from sodium) and a solution of 540 mg. (10% excess) of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole in 10 cc. of dioxane was added during forty-five minutes with shaking at room temperature, thus keeping the methane in excess to prevent self-oxidation of the bromopyrrole. The dropping funnel was washed with 10 cc. of dioxane. The flask was allowed to stand for two hours in the dark and then placed in the ice-box for one hour. The crystalline precipitate was filtered off and washed with 5 cc. of dioxane; yield 380 mg. or 45%.

The free base was prepared by grinding with dilute ammonia solution. Recrystallization from hexane gave red needles melting with decomposition at 190° and identified as 3,5,3′,5′-tetramethyl-4,4′-dicarbethoxydipyrrylmethene (XI).

A control reaction was run in which the dipyrrylmethane was omitted but the bromopyrrole was present. No precipitate was obtained, indicating that none of the product formed in the first reaction came from the self-oxidation of the bromopyrrole.

3,5,3′,5′,4″-Pentamethyl-4,4′,3″-tricarbethoxy-5″-bromotripyrrylmethane (XII).—Eight hundred twenty milligrams (0.002 mole) of 3,5,4′-trimethyl-4,3′-dicarbethoxy-5′-bromodipyrrylmethene was suspended in 80 cc. of ether (distilled from sodium), a solution of 368 mg. (0.0022 mole) of 2,4-dimethyl-3-carbethoxypyrrole in 10 cc. of ether was added rapidly. The flask was tightly stoppered, protected from light and shaken until all of the methene went into solution. The reaction mixture was allowed to stand in the ice-box overnight. Filtration and washing with 20 cc. of ether gave a pure product decomposing at 209°; yield, 1.10 g. or 95.5%. Recrystallization from alcohol–water yielded a product melting with decomposition at 210°.

Anal. Calcd. for $C_{27}H_{34}O_6N_3Br$: C, 56.25; H, 5.94. Found: C, 56.29; H, 5.90.

Rapid Cleavage of Tripyrrylmethane XII.—Nine hundred milligrams of 3,5,3′,5′,4″-pentamethyl-4,4′,3″-tricarbethoxy-5″-bromotripyrrylmethane was suspended in 225 cc. of dry diethyl ether, cooled to 0° and a stream of dry. gaseous hydrogen chloride passed in for one-half hour. The flask was allowed to stand in an ice-box overnight after which the precipitated product was filtered off and washed with a little ether; yield, 510 mg. or 73%.

The free base was prepared by grinding with dilute ammonia solution. Recrystallization from hexane gave a product melting with decomposition at 153°, identified as 3,5,4′-trimethyl-4,3′-dicarbethoxy-5′-bromodipyrrylmethene.

Slow Cleavage of Tripyrrylmethane XII.—One and five hundredths grams of 3,5,3′,5′,4″-pentamethyl-4,4′,3″-tricarbethoxy-5″-bromotripyrrylmethane was dissolved in 60 cc. of glacial acid, warmed to 40° and a drop of 48% hydrobromic acid was added every fifteen minutes until a total of ten drops had been added. The solution was cooled to 33°, 30 cc. of ether added and the flask allowed to stand in an ice-box for fourteen hours. The solid material was filtered off and washed with 20 cc. of ether; yield, 0.330 g. or 43%.

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(14) Fischer and Ernst, *Ann.*, **447**, (a) 159, (b) 147 (1926).

The free base was prepared by grinding with dilute ammonia solution. Recrystallization from hexane–benzene gave red needles melting with decomposition at 185°. A second recrystallization raised the melting point to 189°. Catalytic hydrogenation gave a light yellow solid melting with slight decomposition at 229–230°. A mixed melting point with dipyrrylmethane XV gave no depression. This identified the methene free base as 3,5,3′,5′-tetramethyl-4,4′-dicarbethoxydipyrrylmethene.

Conversion of Dipyrrylmethene V to Dipyrrylmethene XI by the Action of 2,4-Dimethyl-3-carbethoxypyrrole and Hydrogen Bromide.—Four hundred ninety milligrams of 3,5,4′ - trimethyl - 4,3′ - dicarbethoxy - 5′ - bromodipyrrylmethene hydrobromide and 167 mg. of 2,4-dimethyl-3-carbethoxypyrrole were dissolved in 50 cc. of glacial acetic acid, warmed to 50° and five drops of 48% hydrobromic acid solution were added. After standing for fifty minutes at 50°, the solution was allowed to cool slowly to room temperature. After eight hours, the red crystalline product was filtered off and washed with 10 cc. of ether; yield, 110 mg. or 26%. The free base was prepared by grinding with dilute ammonia solution. Recrystallization from hexane gave a product decomposing at 189°, identified as the free base of methene XI.

A similar experiment was performed omitting the 2,4-dimethyl-3-carbethoxy pyrrole. The bromomethene hydrobromide V was recovered unchanged.

3,5,3′,5′,4″-Pentamethyl-4,4′,3″-tricarbethoxytripyrrylmethane (XVIII).—Three hundred ten milligrams of 3,5,3′,5′,4″-pentamethyl-4,4′,3″-tricarbethoxy-5″-bromotripyrrylmethane (XII) was dissolved in 20 cc. of pure, synthetic methanol in a 50-cc. boiling flask equipped with a sulfur-free rubber stopper and an inlet tube; 15 mg. of magnesium oxide, 500 mg. of Norite A and 8 drops of 10% palladium chloride solution were added and the mixture shaken under two atmospheres of hydrogen for forty-five minutes. When reduction was complete, the solution was heated to boiling and filtered while hot. The filtrate was evaporated to a volume of 10 cc. and water was added until the solution became slightly turbid. After cooling, the new tripyrrylmethane was filtered off and washed with water; yield, 160 mg. or 60%. The sample darkened at 217° and melted with decomposition at 224°. Recrystallization from alcohol–water gave a pure product melting at 224–225°.

Anal. Calcd. for $C_{27}H_{35}O_6N_3$: C, 65.17; H, 7.09. Found; C, 64.95; H, 7.03.

Preparation of 2-Formyl-3-methyl-4-carbethoxypyrrole (XXI). (a) **3-Carbethoxy-4-methyl-5-carboxylpyrrole.**—Three and four-hundredths grams of 2,4-dicarbethoxy-3-methylpyrrole[12b] and 1.0 g. of potassium hydroxide were dissolved in 60 cc. of 80% ethanol and refluxed for two and one-half hours. The solution was then poured slowly, with agitation, into 400 cc. of ice-water mixture. After standing in an ice-box for about two hours, the unhydrolyzed starting material was filtered off and the filtrate was acidified with hydrochloric acid to the congo red endpoint. The acid was filtered off, washed with water until free from chlorides and dried in an oven at 75°; yield, 2.35 g. or 92.3%. The acid decomposes with evolution of carbon dioxide at about 230°. The pyrrole crystallizes from acetone–water in long, colorless needles.

Anal.[15] Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.62. Found: C, 54.64; H, 5.67.

(b) **3-Methyl-4-carbethoxypyrrole.**[13b]—Ten grams of 3-carbethoxy-4-methyl-5-carboxylpyrrole was placed in a 250 cc. distilling flask and mixed with sufficient dry glycerol to form a paste. With a 125-cc. distilling flask acting as a receiver (water-cooled) the pyrrole was heated rapidly until the boiling point of glycerol was reached. Most of the product distilled between 220 and 260°. After the receiver had cooled to about 60°, alcohol was added with warming until the mixture became homogeneous. The alcoholic solution was then poured with stirring into five times its volume of a mixture of ice and water, allowed to stand in an ice-box for two hours and the 3-methyl-4-carbethoxypyrrole was filtered off and washed with water; yield, 3.55 g. or 46%; m. p. 73° (uncor.).

The product may be recrystallized from alcohol–water if necessary.

Attempts to increase the yield on this decarboxylation failed. In spite of the low yield, the product was good and there was little tarring.

(c) **2-Formyl-3-methyl-4-carbethoxypyrrole (XXI).**—The directions given by Fischer and Wiedemann[13c] are adequate; yield, 74%; m. p. 117–118°. Recrystallization from water yielded beautiful long needles melting at 122°.

3,5,3′-Trimethyl-4,4′-dicarbethoxydipyrrylmethene Hydrochloride (XXII).[13a]—Five hundred forty-three milligrams of 2-formyl-3-methyl-4-carbethoxypyrrole and 501 mg. of 2,4-dimethyl-3-carbethoxypyrrole were dissolved in 30 cc. of ether (distilled from sodium) cooled to 0° and a stream of dry, gaseous hydrogen chloride passed in for fifteen minutes. After standing for one hour the red solid was filtered off and washed with ether; yield, 920 mg. or 56%.

The free base was prepared as usual with dilute ammonia. Recrystallization from hexane gave a product melting with decomposition at 147°.

3,5,3′-Trimethyl-4,4′-dicarbethoxy-5′-bromodipyrrylmethene Hydrobromide (XVII).—Eight hundred milligrams of 3,5,3′-trimethyl-4,4′-dicarbethoxy dipyrrylmethene hydrobromide was suspended in 60 cc. of glacial acetic acid and 1.5 cc. of a solution of bromine in glacial acetic acid (0.31 g./cc.) was added dropwise with shaking at 50°, and the temperature was raised slowly until all of the methene had gone into solution. On cooling to room temperature, small red crystals separated which were filtered off and washed with 5 cc. of acetic acid; yield, 580 mg. or 61%.

The free base was made in the usual manner with dilute ammonia. Recrystallization from hexane gave a product melting with decomposition at 151°.

Anal. Calcd. for $C_{18}H_{21}O_4N_2Br$: C, 52.82; H, 5.17. Found: C, 52.90; H, 5.13.

3,5,3′,5′,3″-Pentamethyl-4,4′,4″-tricarbethoxytripyrrylmethane (XXIII).—Three hundred twenty-seven milligrams of 3,5,3′-trimethyl-4,4′-dicarbethoxydipyrrylmethene was suspended in 50 cc. of ether (distilled from sodium), a solution of 184 mg. of 2,4-dimethyl-3-carbethoxypyrrole in 15 cc. of ether (distilled from sodium) and a small crystal of potassium acid sulfate were added quickly and the flask tightly stoppered. After standing for three hours at room temperature with occasional shaking, all of the methene had gone into solution and a white solid had started to separate. The flask was allowed to stand in an ice-box for three hours and the crude product was filtered off and washed with 15 cc. of ether; m. p. 205° with decomposition. Two recrystallizations from alcohol–water raised the decomposition point to 222°.

When mixed with its structural isomer, 3,5,3′,5′,4″-pentamethyl-4,4′,3″-tricarbethoxytripyrrylmethane, the melting point was 202°, showing lack of identity.

Anal. Calcd. for $C_{27}H_{35}O_6N_3$: C, 65.17; H, 7.09. Found: C, 65.13; H, 7.04.

Summary

The paper presents a study of the condensation of α-free-α-methylpyrroles to 5-methyl-5′-bromodipyrrylmethenes by means of bromine.

1. The sequence of the consecutive reactions in the condensation is established by isolation of the individual reactions, analogies and rate studies.

2. A new dipyrrylmethene synthesis is reported.

3. A condensation and self-oxidation of a bromopyrrole catalyzed by hydrogen bromide which competes with the bromine-induced condensation is reported.

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(15) Performed by J. L. Straughn.

4. Two alternative schemes of consecutive reactions are proposed to account for the self-oxidation reaction.

5. The ring-bound halogen of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole is shown to have the oxidizing properties of a "positive halogen" atom.

6. A tripyrrylmethane is synthesized which can cleave to give two different dipyrrylmethenes, depending upon the condition of the reaction.

7. A dipyrrylmethene is converted into another dipyrrylmethene in a new type of "displacement reaction."

8. Further evidence is given to establish the structure of 3,5,4'-trimethyl-4,3'-dicarbethoxy-5'-bromo dipyrrylmethene.

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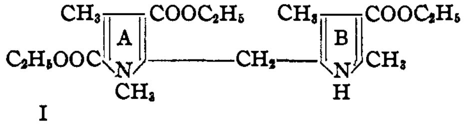
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

An Anomalous Reaction of Dipyrrylmethanes Leading to a New Class of Heterocyclic Compounds[1,2]

BY ALSOPH H. CORWIN AND RUDOLPH C. ELLINGSON[3]

In an investigation of the methylation of dipyrrylmethanes, Corwin, Bailey and Viohl[4] noted the development of a deep blue fluorescence upon treating 1,4,3',5'-tetramethyl-3,5,4'-tricarbethoxy dipyrrylmethane (I) with sodium. Corwin and Ellingson[5a] reported the isolation and analysis of the compound responsible for this effect and found that it could result from the elimination of the elements of ethanol from the dipyrrylmethane. Similar compounds are also reported by Corwin and Buc,[6] who develop additional methods for their investigation in the accompanying paper.



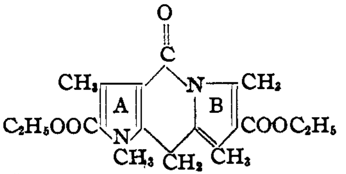
I

Compounds of this new class have aroused interest in the laboratory because their color and fluorescence in organic solvents markedly resemble those of crude oil. Since decomposition products of chlorophyll might conceivably be responsible for the fluorescence of crude oils and might also be related to these synthetic products, the possibility exists that analogs of these synthetic products occur in nature. Both for this reason and to clarify the mechanisms of the reactions involved, we deemed it worth while to investigate the structure of these substances.

It was found that the condensation reaction could be carried out conveniently in dioxane with sodium triphenylmethyl as a catalyst but that it failed in benzene in which the sodium salt of the dipyrrylmethane is insoluble. The reaction also fails if the 1-position is unmethylated or if a methyl group is in the 1'-position. The condensation is distinctly an anomalous reaction of dipyrrylmethanes since it is absent in the great majority of these substances studied.

The condensation product failed to react with phenylhydrazine, hydroxylamine and semicarbazide. This indicates that a true keto group is not present in the molecule. There are, however, ketones such as dipyrryl ketones and hindered aliphatic and aromatic ketones which fail to show the usual ketonic reactions.

The compound was titrated with sodium triphenylmethyl to determine the number of active hydrogen atoms present.[5c] A color indicative of an end-point was obtained as soon as the solvent blank had been passed in the titration, but this color is much deeper than that of sodium triphenylmethyl, itself. This same deep violet-red color appears during the formation of these compounds when sodium triphenylmethyl is the condensation catalyst. We attribute this color to the formation of a carbanion from the condensation product by the action of sodium triphenylmethyl and hence to the absence of an active N-H linkage and the presence of an active C-H linkage. These facts suggest that the observed elimination of ethanol involves the hydrogen atom originally present on Ring B of dipyrrylmethane I and strongly suggest that the compound has the structure of formula II. This conclusion is supported by the fact that methylation of the nitrogen on Ring B of dipyrrylmethane I blocks the reaction.



II 204°

The ring system postulated in structure II is new.

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[1] Studies in the Pyrrole Series, XIII; Paper XII, Corwin and Viohl, THIS JOURNAL, **66**, 1137 (1944).

[2] This paper is from the doctoral dissertation of Rudolph C. Ellingson, The Johns Hopkins University, 1938, and was presented in part at the Boston Meeting of the American Chemical Society, September, 1939.

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[4] Corwin, Bailey and Viohl, THIS JOURNAL, **64**, 1271 (1942).

[5] Corwin and Ellingson, *ibid.*, (a) 2106, (b) 2101, (c) 2098 (1942).

[6] Corwin and Buc, *ibid.*, **66**, 1151 (1944).