

immediately. Within a few minutes the sodium salt of the dipyrromethane had dissolved. The flask was allowed to stand overnight and the product isolated in the usual manner; yield, 210 mg. of crude material which after two crystallizations from hexane melted at 125°; no depression with methane XXIII, m. p. 129°.

C. Condensation Reaction in Dioxane.³—Five hundred and fifteen milligrams (0.00123 mole) of methane XXII was dissolved in 10 cc. of dioxane and treated with 0.00123 mole of sodium triphenylmethyl. After the first drop of reagent had been added, the blue fluorescence noted above appeared. As the addition progressed the solution became cherry-red and finally deep violet. No precipitate was deposited. After ten minutes the flask was removed and the contents poured into water. The violet color disappeared leaving a yellow ether-benzene layer with a blue fluorescence. The mixture was warmed to remove the ether and benzene, cooled, filtered and the yellow solid extracted with hexane, leaving 430 mg. of a yellow powder which melted at 150–192°. After crystallizing twice from ethanol the compound melted at 203–204°; yield, 300–400 mg.

Anal. Calcd. for C₃₀H₂₄N₂O₆: C, 64.50; H, 6.49; mol. wt., 372. Found: C, 64.46, 64.44; H, 6.40, 6.43; mol. wt., 388, 369, 379 (b. p. elevation in chloroform).

When the violet solution was treated with dimethyl sulfate, the deep color disappeared immediately but the compound isolated from the reaction was identical with

that prepared above. Evidently this material shows a resistance to methylation similar to that of methane XII.

Summary

1. It is shown that a standardized solution of sodium triphenylmethyl may be used to titrate for active hydrogens.

2. This reagent is inert to ester groups, C–Br links and most CH groups.

3. The >CH–CO– linkage is active to sodium triphenylmethyl.

4. The reagent permits a check upon possible condensations by regeneration of the starting material.

5. A dipyrromethane with a bridge hydrogen acidic to sodium triphenylmethyl has been discovered.

6. Titration followed by methylation has been used to confirm the structures of a number of dipyrromethanes.

7. A method for specific, selective methylation of bifunctional weak acids is presented.

8. A new pyrrole condensation is recorded.

BALTIMORE, MARYLAND

RECEIVED MAY 28, 1942

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

Rearrangements of Pyrrole Rings in the Oxidation of Dipyrromethanes¹

BY ALSOPH H. CORWIN AND KARL J. BRUNINGS²

Previous papers of this series³ have developed the fact that certain pyrrole-carbon single bonds which can cleave to give stable resonating systems are rapidly split by acid at room temperature and below. Brunings and Corwin⁴ extended this study with the observation that, under even milder conditions, it is possible to cleave a pyrrole-carbon bond belonging to the resonating system of a pyrrole pigment. This observation provides a starting point for the systematic study of pyrrole pigments which may be of significance with respect to the catabolic processes which these substances undergo in biological systems. The conversion of hemoglobin to bile pigments and the

problem of the reactions causing varying sequences of substituents on naturally occurring porphyrins are examples of fundamental biological processes which may be elucidated by studies upon the stability of variously substituted pigments. This paper reports a study of an even readier cleavage of a pyrrole pigment system than that previously discussed.

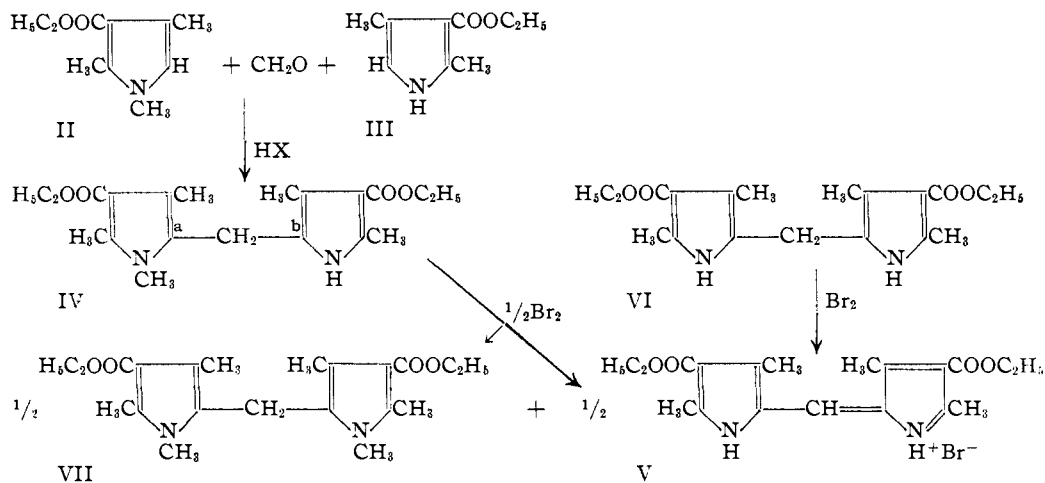
Our earlier papers show that attempts to prepare mono-N-methyldipyrromethenes by the condensation of pyrrole aldehydes with α -free pyrroles yield either symmetrical N-free methenes or products which have not been identified. That this peculiarity is not due to the impossibility of preparing an N-methyl methene was demonstrated by the preparation of 1,3,5,1',3',5'-hexamethyl-4,4'-dicarbethoxydipyrromethene salts (I).⁴ Among the reactions generally used in dipyrromethene synthesis, the oxidation of dipyrromethanes would appear to be the most reliable for preparing and establishing the structures of

(1) Studies in the Pyrrole Series. X. Paper IX. Corwin and Ellingson, *THIS JOURNAL*, **64**, 2098 (1942).

(2) A portion of this paper is taken from the doctoral dissertation of Karl J. Brunings, The Johns Hopkins University, 1939, and was presented at the Baltimore Meeting of the American Chemical Society in April, 1939.

(3) Corwin and Andrews, *THIS JOURNAL*, **56**, 1086 (1936); Andrews and Corwin, *ibid.*, **59**, 1973 (1937); Paden, Corwin and Bailey, *ibid.*, **62**, 418 (1940).

(4) Brunings and Corwin, *ibid.*, **64**, 593 (1942).



these pigments. This method was successful in the preparation of methene I.

To study mono-*N*-methylmethane bromination on a comparable system, 1,3,5,3',5'-pentamethyl-4,4'-dicarboxydipyrrolylmethane (IV, Chart I) was prepared by the unsymmetrical condensation of the *N*-methylated and NH α -free pyrroles II and III (Chart I) with formaldehyde. The methane was then brominated under the conditions that had successfully produced the di-*N*-methylmethene (I). Instead of the expected mono-*N*-methylmethene (XIII, Chart II) the symmetrical di-NH-methene (V) was obtained in about 60% yield based on the amount of NH-pyrrole ring in the starting methane (IV). Investigation of the mother liquor showed that 1,3,5-trimethyl-2-bromo-4-carboxypyrrole (XI, Chart II) was a by-product of the reaction. It was then found that by using only one-half mole of bromine with one mole of methane a practically quantitative yield of pure crystalline di-NH-methene (V) was obtained. Di-*N*-methyl dipyrrolylmethane (VII) was isolated from the mother liquor. The di-NH-methene (V) obtained by this anomalous reaction may be prepared in quantitative yield by the bromination of the corresponding di-NH-methene (VI). These reactions are given in Chart I.

The possibility that the dipyrrolylmethane (IV) might be a mixture of the unmethylated and di-*N*-methylated methanes (VI and VII) was excluded by bromination of actual mixtures of the two symmetrical methanes and by a thorough investigation of the structure of this compound.¹ Any explanation based on the removal of the methyl groups from the nitrogens is excluded by the isolation of the di-*N*-methyl methane (VII) and *N*-

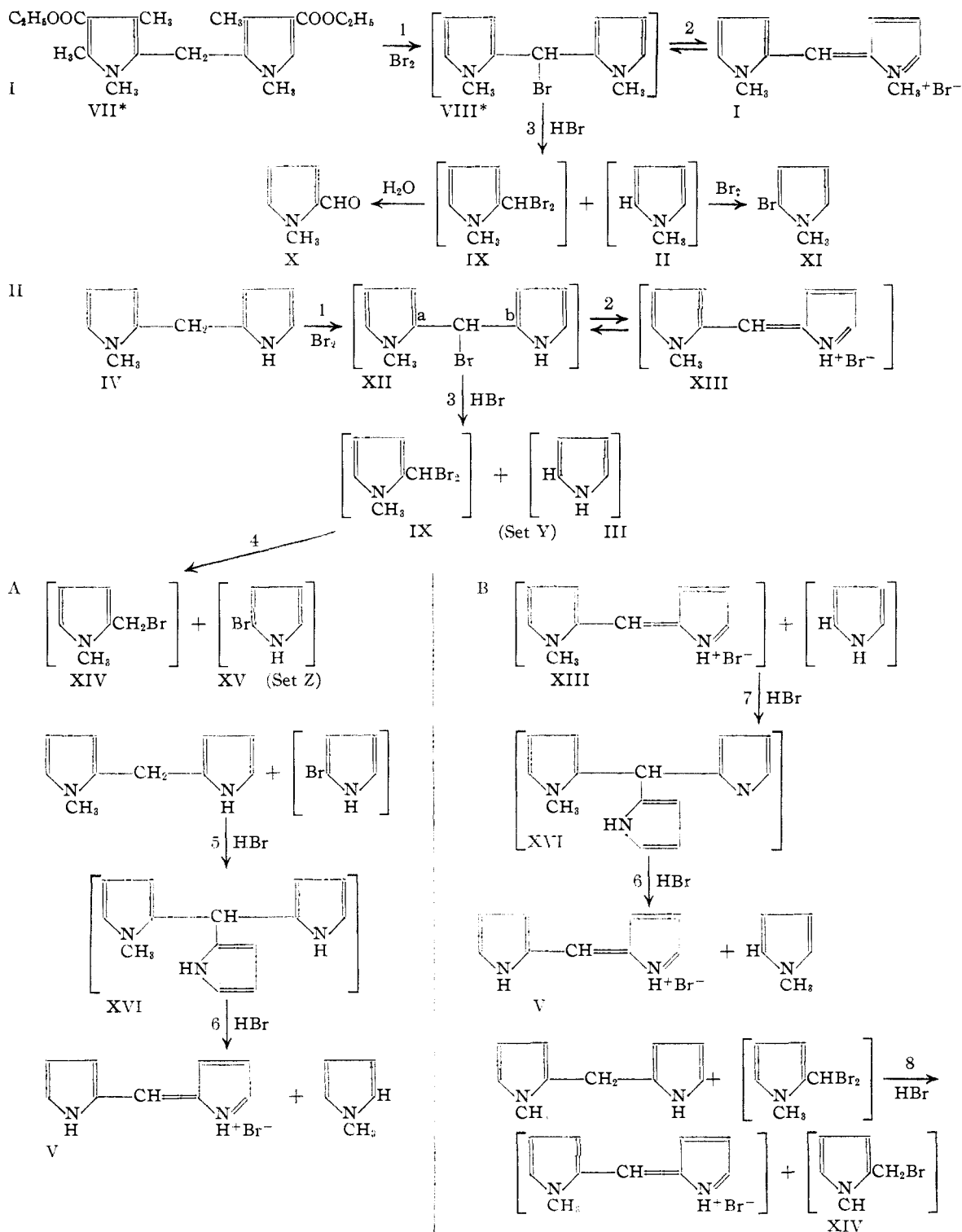
methyl- α -bromopyrrole (XI) as by-products of the half-molar and molar brominations, respectively, and by the quantitative yield based on the amount of NH-pyrrole in the starting methane.

Assured then of the structure of the starting dipyrrolylmethane and the stability of the methyl groups on the nitrogens, it is apparent that a cleavage of the C-C bond (IV, a or b) takes place. The motivating force of the reaction is supplied by the hydrobromic acid. Realizing the possibility of acid cleavage, a score of oxidation reactions in neutral and basic medium were tried in an effort to obtain the mono-*N*-methylmethene. In every case either no reaction occurred or the methane was degraded to products no longer identifiable as pyrrole derivatives. On the other hand, acidic oxidizing agents of low activity, *e. g.*, formic acid or oxygen and mineral acid, are capable of giving the reaction. The rate and completeness of the reaction depend both on the oxidizing agent and the strength of the acid. For example, air in the presence of hydrobromic acid gives a low yield of the methene (V) at a slow rate, while the bromination gives a 75% yield in less than five minutes. The rate of bromine consumption is too fast to measure with accuracy by ordinary techniques. Chlorination results in a rather complete and very rapid reaction but the rate of appearance of the methene is slow.

Cleavage of a dipyrrolylmethene system to pyrrole fragments has been shown to take place as a by-reaction in the bromination of the di-*N*-methylmethane (VII) to the corresponding methene (I) in paper VI of this series. Evidence was presented there to show that the steric interference

of the methyl groups on the nitrogens reduces the stability of the methene system. Although the steric interference between the methyl group and the hydrogen in the mono-*N*-methylmethene

would be considerably less, the lack of symmetry in the Kekulé resonance forms would also lead to a decrease in the stability of the dipyrromethene system. Finally, the possibility of the pyrrole



A and B

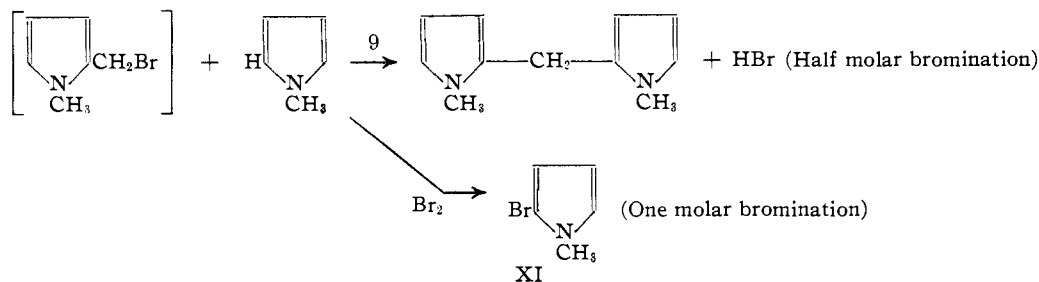


CHART II.

* The substituents present in the 3, 4 and 5 positions of compound VII are understood to be present on all the remaining pyrrole rings of the chart.

fragments forming insoluble crystalline end-products might be expected to bring about complete cleavage by disturbance of the equilibria.

Fischer and Riedl⁵ have demonstrated acid cleavage of two unsymmetrical dipyrrolymethanes under non-oxidizing conditions, and thus the possibility of cleavage of the methane by hydrobromic acid produced in the early stages of the reaction must also be considered in formulating a mechanism for the anomalous bromination of mono-N-methyldipyrrolymethane IV. This alternative may be shown to be untenable by tests on the stability of the methane in the presence of hydrobromic acid under conditions considerably more drastic than those of the bromination. In order to test for cleavage products the methane dissolved in alcohol was boiled with formaldehyde in the presence of both hydrochloric and hydrobromic acids. If the bonds *a* or *b* were broken under this treatment, α -free pyrrole II or III would result. Since both the NH- and N-methylpyrroles condense with formaldehyde to produce dipyrrolymethanes, the mono-N-methylmethane would disproportionate to the di-NH- (VI) and the di-N-methyl- (VII) methanes. Such a disproportionation was not observed.

The di-NH-methene and N-methylpyrrole fragments are also obtained when the mono-N-methylmethane is treated with formic acid in the presence of hydrobromic acid. This reaction might be formulated as resulting from a condensation of formic acid with the α -free pyrrole produced by acid cleavage, a standard methene condensation. However, it can be shown that this explanation is not valid, since formic acid will not condense with the α -free NH-pyrrole under the conditions of the reaction. These experiments show that the cleavage does not occur on the methane and thus ox-

idation of the methane must be the initial reaction of the bromination.

The extremely fast rate of the reaction and the failure of all methods intended to stop the reaction after the initial bromination make isolation of NH-intermediates in the formation of the di-NH-methene (V) impossible. However, in the case of the bromination of the di-N-methylmethane (VII), previously referred to,⁴ the pyrrole fragments resulting from cleavage are actually isolated in addition to the expected di-N-methylmethene from the normal oxidation. Moreover, this reaction lends itself to careful study and evidence has been presented⁴ to show that the cleavage does not occur on the methene salt but on an intermediate in the bromination. The chemical and physical properties of the sterically hindered methene suggested that the covalent dipyrrolylmethyl bromide (VIII, Chart II) is the intermediate in the reaction. The steps involved in the cleavage of the di-N-methylmethane are given in the first series of reactions in Chart II.

If one assumes that the cleavage of the mono-N-methylmethane proceeds analogously to that of the di-N-methyl system, the problem of setting up a mechanism becomes one of finding established reactions involving the pyrrole derivatives which may be present in the bromination solution and which will produce the di-NH-methene (V) and the N-methylated by-products. Two alternative mechanisms, A and B, are described in the second series of reactions in Chart II. Reactions 1, 2 and 3 of this series are identical with those of the di-N-methyl system in the first series. Cleavage of the dipyrrolylmethyl bromide (XII) is postulated to occur at bond *b* to give the α -dibromomethyl pyrrole (IX) and the α -free pyrrole (III) (Set Y), since cleavage at bond *a* would yield pyrrole fragments which cannot condense according to known

(5) Fischer and Riedl, *Z. physiol. Chem.*, **207**, 200 (1932).

reactions to produce the products obtained in the bromination.

One mole of bromine cleaves two moles of the methane in the over-all reaction, and, therefore, one of the cleavage products must react with the starting methane (IV). In mechanism A this reaction is preceded by a disproportionation of the primary cleavage products (Reaction 4) to yield α -bromomethylpyrrole (XIV) and the α -bromopyrrole (XV) (Set Z). Reactions of this type have not been studied as yet in the pyrrole series since dihalomethyl derivatives are very difficult to prepare. However, it is reasonable to assume that the intermediate bromopyrrole would be a very good brominating agent and it can be shown that the α -free pyrrole brominates with extreme rapidity. The reaction between the mono-N-methylmethane (IV) and the α -bromopyrrole (XV) (Reaction 5) can be carried out under the conditions of the bromination to give a quantitative yield of the di-NH-methene (V) with a rate which is compatible with that of the bromination. In analogy to similar reactions in the pyrrole series it is reasonable that this reaction should have tripyrrylmethane (XVI) as an intermediate. The cleavage of this tripyrrylmethane with hydrogen bromide (Reaction 6) has also been carried out under comparable conditions³ to give the expected methene (V) with both the rate and the yield in agreement with those of the bromination. The N-methyl α -free pyrrole (II) has been isolated from both reactions.

The fundamental reaction of the alternative mechanism B is the condensation of the primary cleavage product, the α -free pyrrole (III) and the mono-N-methyldipyrrylmethene (XIII) (Reaction 7) to yield the di-NH-methene (V) through the tripyrrylmethane (XVI). Since the methene (XIII) has not been isolated, this reaction could not be imitated. However, the condensation has well-established analogies in the pyrrole series and its mechanism has been thoroughly worked out.³ As described above, Reaction 6 may be carried out under conditions of the bromination. The reactions thus far account for only one-half of the yield of the di-NH-methene and, therefore, another oxidation of the starting methane must occur. The dibromomethylpyrrole (IX) is the only oxidizing agent remaining and thus Reaction 8 is postulated to provide an additional mole of mono-N-methylmethene which then reacts according to the preceding scheme, leading to a chain

mechanism. This reaction is without analogy in the pyrrole series for the reasons mentioned above. However, the oxidizing action of this type of dihalomethyl derivative can be demonstrated by the reaction between 2-dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole and the mono-N-methylmethane (IV) which again yields the anomalous di-NH-methene. This reaction is very slow and incomplete, a behavior which might be predicted on the basis of the effect of the carbethoxy groups on the pyrrole ring.

Common to both mechanisms (A and B) is the final reaction 9 which accounts for the isolation of the di-N-methylmethane (VII) from the bromination reaction. The isolation of the α -free pyrrole from the formic acid oxidation and the incomplete yield of the di-N-methyl methane from the bromination are in agreement with the generally slow rate of this methane condensation.

Essentially, the question as to which of these two proposed mechanisms is the correct one becomes a problem of determining whether the α -free pyrrole (III) or the starting methane (IV) reacts more rapidly with the dibromomethylpyrrole (IX). Lacking the dibromomethylpyrrole, a selection between the two mechanisms can only be made on indirect evidence. No difference in bromination rate of the pyrrole and methane could be found by the techniques at our disposal, both reactions going to completion in less than five seconds. It is significant, however, that in the cleavage of the di-N-methyl system, α -free pyrrole is never isolated. This is easily interpreted by assuming that the rate of bromination (k_b) of the pyrrole is faster than that of the methane (k_1). It must be pointed out, however, that the comparative rates of bromination may depend upon the type of brominating agent in question and thus might be reversed in going from bromine to α -dibromomethylpyrrole.

Strong positive support is given mechanism A by the low yields obtained when one mole of bromine per mole of methane is employed. In mechanism A the formation of methene depends on the presence of unoxidized starting methane (Reaction 5), while in mechanism B the methene is formed from the oxidation intermediate (XIII) and one of its cleavage products (Reaction 7). Therefore the use of an extra half mole of bromine should either give no methene or at least a greatly diminished yield if mechanism A is valid. According to mechanism B, however, one molar bromina-

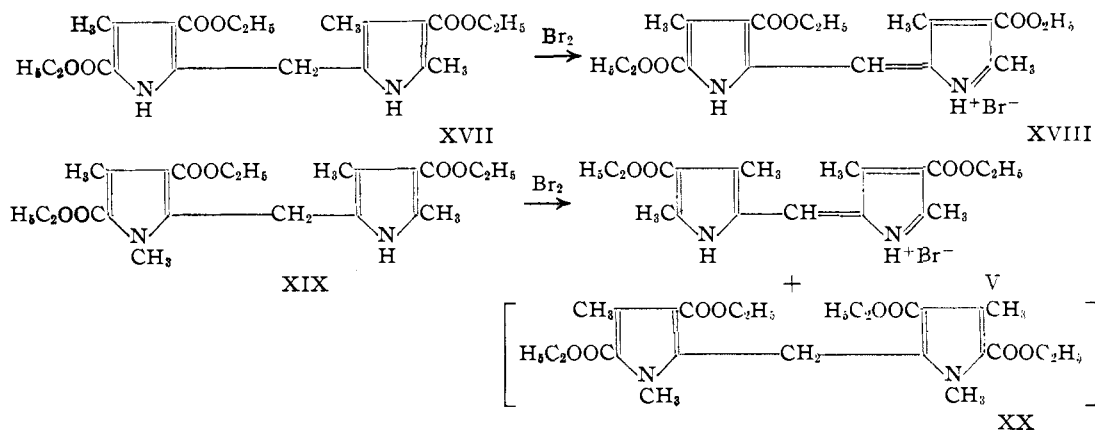


CHART III.

tion should not affect the yield of methene but rather the state of oxidation of the pyrrole fragments. Actually, the yield is depressed almost a half and a considerable amount of unidentifiable by-product is obtained. The fact that a 60% yield of the methene is obtained instead of one mole of α -bromomethylpyrrole (XIV) and one mole of the α -bromopyrrole (XV) may be accounted for by the rapidity with which the bromopyrrole-dipyrromethane condensation (Reaction 5) takes place.

Until the mono-N-methylmethene can be prepared and its properties studied, the validity of either one of these mechanisms cannot be uniquely established. It is possible, of course, that both mechanisms operate, the importance of each depending on the conditions under which the bromination is carried out. As indicated above, dibromomethylpyrrole derivatives are unknown and a study of their properties would do much toward elucidating the present unusual reaction.

The anomalous course of the bromination of the mono-N-methylmethane must destroy our confidence in the absolute reliability of this synthetic method as a proof of the structure of dipyrromethenes. In order to determine whether this anomalous reaction is in any way general for unsymmetrical methanes, a series of dipyrromethanes⁶ was subjected to bromination. Of those tried, one other example, the 1,4,3',5'-tetramethyl-3,5,4'-tricarboethoxydipyrromethane (XIX, Chart III) was observed to give the symmetrical methene (V). Bromination of the di-NH-methene (XVII) of the corresponding configuration gave a normal result, while the methane having a methyl group on the other pyrrole ring

yielded unidentifiable products. The reactions are given in Chart III.

The oxidation of unsymmetrical dipyrromethanes has not been extensively employed as a method of preparing dipyrromethenes. However, in a few cases the method has been applied^{7,8} successfully to give normal results. On the basis of the studies made on the mono-N-methyl and the di-N-methyl systems,⁴ it may be stated that an anomalous course of the methane bromination may be looked for whenever there is reason to believe that the corresponding methene will be unstable. Unfortunately, no reliable criteria exist for predicting the stability of dipyrromethenes. The three examples which have been shown to be subject to acid cleavage all contain methyl groups on the nitrogens and it has been shown that the steric interference of these groups gives rise to a reduction in the stability of the dipyrromethenes. Lack of symmetry and the electrical effect of groups on the pyrrole rings are other factors which must be considered in predicting the stability of dipyrromethenes but their use must await an orderly correlation of the physical and chemical properties of the many dipyrromethenes now available.

The authors wish to express their appreciation to the Rockefeller Foundation which has supported a portion of this investigation.

The junior author also wishes to acknowledge a grant-in-aid from the Hynson, Westcott and Dunning Fund.

Experimental Section

Preparation of 1,3,5,3',5'-Pentamethyl-4,4'-dicarboethoxydipyrromethane (IV).—A solution of 20 g. of 1,2,4-

(7) Fischer and Adler, *Z. physiol. Chem.*, **200**, 220 (1931).

(8) Fischer and Baumler, *Ann.*, **468**, 74 (1929).

(6) Corwin and Quattlebaum, *This Journal*, **64**, 922 (1942).

trimethyl-3-carbethoxyppyrrrole (II) in 100 cc. of alcohol and a solution of 20 g. of 2,4-dimethyl-3-carbethoxyppyrrrole (III) in 100 cc. of alcohol are mixed in a 500-cc. Erlenmeyer flask and 28 cc. of formalin added. After the temperature has been raised to 45°, 10 cc. of concentrated hydrochloric acid is run in. The temperature is kept below 60° by cooling the flask from time to time in running water. After standing in the cold for several hours, 40 g. of crude product is filtered from the mixture and washed with cold 50% alcohol-water. The material is then refluxed in 50% alcohol-water for one hour and again filtered. Recrystallization of the precipitate from alcohol yields 30 g. of large crystalline plates, melting irresolvably at 178-179°; yield, 75%. Mixed melt with mono-N-methyldipyrromethane prepared by Dr. R. C. Ellingson by a different method,¹ 178-179°.

One Molar Bromination of Mono-N-methyldipyrromethane (IV).—A solution of 100 mg. of the mono-N-methylmethane (IV) in 10 cc. of dry carbon tetrachloride is placed in a 25-cc. Erlenmeyer flask; 0.05 g. of bromine dissolved in 0.5 cc. of carbon tetrachloride is added quickly while the flask is vigorously twirled. The mixture is allowed to stand several hours in the cold to ensure complete precipitation and then filtered; 35 mg. (58% of the theoretical) of yellow methene-like needles is obtained. This material on treatment with concentrated ammonia and subsequent recrystallization from hexane-benzene yields long red needles, melting with decomposition at 189-190°. Mixed melt with 3,5,3',5'-tetramethyl-5,5'-dicarbethoxydipyrromethene (V), 189-190° with decomposition. Reduction of the original product with palladium-hydrogen gives the dipyrromethane corresponding to the configuration of di-NH-methene V.

Isolation of 1,3,5-Trimethyl-2-bromo-4-carbethoxyppyrrrole (XI) from the One Molar Bromination of Mono-N-methyldipyrromethane IV.—The mono-N-methylmethane (1.5 g.) is dissolved in 150 cc. of dry carbon tetrachloride and placed in a 250-cc. Erlenmeyer flask; 200 cc. of water containing 20 g. of potassium carbonate is placed in a separatory funnel and 0.61 g. of bromine dissolved in 6.1 cc. of carbon tetrachloride is then run into the methane solution quickly and the flask shaken for thirty seconds. The mixture is poured immediately into the separatory funnel containing the potassium carbonate solution and shaken vigorously for several minutes. The carbon tetrachloride layer, which is highly colored, is drawn off and dried with anhydrous potassium carbonate. A chromatograph is then prepared using a six-inch column of activated alumina (150-200 mesh) as adsorbent. The solution is passed through the chromatograph developing a bright yellow band of di-NH-methene V on the alumina. In addition to the yellow band of the di-NH-methene another red band develops indicating an additional methene as by-product. After 200 cc. has been collected, a new receiver is used and additional carbon tetrachloride is passed through until a second fraction of 200 cc. is collected. The first fraction is evaporated to dryness and leaves 125 mg. of fine white needles which melt at 54-55°, decompose with gas evolution at 145-150° and give no depression with N-methyl- α -bromopyrrole (XI).⁴ The second fraction gives a larger amount of solid with a yellow tinge. On warming to about 60° the whole mass turns blood red. If the mix-

ture is not warmed but recrystallized more α -bromopyrrole may be isolated. This behavior is indicative of the presence of another compound. Since the two pyrroles must be equivalent in state of oxidation to a dipyrromethene, the accompanying compound is assumed to be the α -bromomethylpyrrole (XIV, see Chart II). A highly colored third fraction gives a resinous solid which has not been identified.

Half-Molar Bromination of Mono-N-methyldipyrromethane IV.—The methane (1.5 g.) is dissolved in 300 cc. of dry carbon tetrachloride and brominated according to the directions given above using 0.37 g. of bromine in 3.7 cc. of carbon tetrachloride; 850 mg. of fine orange-yellow needles is obtained. When submitted to the tests described in the one molar bromination the product is shown to be di-NH-dipyrromethene V. The yield is 96% of the theoretical based on the amount of NH-pyrrole in the starting methane.

Isolation of 1,3,5,1',3',5'-Hexamethyl-4,4'-dicarbethoxydipyrromethane (VII) from the Half Molar Bromination.—The mother liquor of the above reaction is evaporated in a suction flask at room temperature. The resinous residue is taken up in about 25 cc. of dry hexane, decolorized with Norite A and allowed to crystallize. On repeated recrystallization a colorless compound is obtained; m. p. 156-157°. Mixed melt with 1,3,5,1',3',5'-hexamethyl-4,4'-dicarbethoxydipyrromethane 156-157°.

Oxidation of Mono-N-methyldipyrromethane IV with Formic Acid and Hydrobromic Acid.—A solution of 500 mg. of mono-N-methylmethane IV in 100 cc. of carbon tetrachloride is placed in a 250-cc. glass-stoppered Erlenmeyer flask. After the solution has cooled to room temperature 0.2 cc. of formic acid and 5 cc. of aqueous (45%) hydrobromic acid is run in. The flask is then stoppered, wired and placed on a rotary shaker for four hours. At the end of this time the precipitate of red needles is filtered; yield, 200 mg. The precipitate is ground in a mortar with concentrated ammonia. The free base thus formed is recrystallized from hexane-benzene; m. p. (dec.) 190°; mixed melt with di-NH-dipyrromethene (V) (free base) 190° (dec.).

Reaction of Formic Acid with 2,4-Dimethyl-3-carbethoxyppyrrrole (III).—The α -free pyrrole (III) (230 mg.) is dissolved in 100 cc. of carbon tetrachloride and placed in a 250-cc. Erlenmeyer flask; 0.1 cc. of formic acid and 5 cc. of aqueous hydrobromic acid (45%) are run in as above. After four hours of shaking, no crystals are noted and the color of the solution remains light yellow. On heating to 40° and shaking, the reaction mixture does not change color. If the solution is heated to 65° the solution turns deep red, and on cooling a crop of fine red needles is obtained. The product is the expected di-NH-methene (V).

Isolation of 1,2,4-Trimethyl-3-carbethoxyppyrrrole (II) from Formic Acid Oxidation of Mono-N-methyldipyrromethane IV.—The mono-N-methyl methane (500 mg.) is treated with formic acid and hydrobromic acid in the manner described above. After the methene is filtered off, the carbon tetrachloride solution is shaken with saturated sodium bicarbonate solution, separated and filtered. The filtrate is then evaporated to dryness in a filter flask at room temperature. When the residue appears dry, the

filter flask is fitted with a cold finger and the suction continued while the filter flask is warmed to 60–70° on a water-bath. A heavy coating of N-methyl- α -free pyrrole (II) sublimes onto the cold finger; m. p. 61–62°; mixed melt with N-methyl- α -free pyrrole (II), 61–62°.

Chlorination of Mono-N-methyldipyrrolylmethane IV.—A solution of chlorine in carbon tetrachloride is prepared by bubbling chlorine slowly through dry carbon tetrachloride. The resulting stock solution is stored over calcium chloride in a glass-stoppered Erlenmeyer flask. Just before using, the solution is standardized using excess potassium iodide and titrating with 0.1 *N* thiosulfate solution. The solution used in the present experiment is 0.56 *N*.

A solution of 100 mg. of dipyrrolylmethane IV dissolved in 10 cc. of dry carbon tetrachloride is placed in a 25-cc. Erlenmeyer flask and 1.1 cc. of 0.56 *N* chlorine-carbon tetrachloride (1 mole plus 10%) is added quickly. The solution turns red immediately and then gradually a deep brown. After fifteen minutes fine yellow needles begin to separate; precipitation is complete after standing four hours in the cold. Yield of the di-NH-dipyrrolylmethene (V) hydrochloride is 35 mg. or 70% of the theoretical.

Rate of Bromine and Chlorine Consumption in the Bromination and Chlorination of Mono-N-methyldipyrrolylmethane IV.—The following standard solutions were prepared: (1) 0.0055 *M* mono-N-methylmethane IV in carbon tetrachloride; (2) 0.0284 *N* bromine in carbon tetrachloride; (3) 0.028 *N* chlorine in carbon tetrachloride; (4) 0.0300 *N* thiosulfate solution.

Approximately 1 g. of potassium iodide was dissolved in 20 cc. of concentrated acetic acid in a 50-cc. glass-stoppered Erlenmeyer flask; 10 cc. of the 0.0055 *M* mono-N-methylmethane solution was pipetted into a 50-cc. glass-stoppered Erlenmeyer flask. To this solution 3.9 cc. of the 0.0284 *N* bromine solution (1 mole) was added quickly, the flask shaken vigorously for five seconds and the potassium iodide solution added immediately. The flask was shaken again and the resulting solution titrated with 0.0300 *N* thiosulfate solution, using starch as an indicator; 3.0% of the bromine remained, indicating 97% consumption in five seconds. A series of experiments gave values ranging from 96–100% consumption of bromine in five seconds.

A similar experiment was run using 11.7 cc. of the standard bromine solution (3 moles). The reaction was terminated after five seconds as described above. Titration with standard thiosulfate solution showed that 92% of 2 moles of bromine had been consumed.

Identical rate measurements were made on the di-N-methyldipyrrolylmethane (VII) and the corresponding di-NH-methane (VI). No difference could be observed between the rates of bromine consumption of the di-N-methyl and the mono-N-methyldipyrrolylmethanes. A slightly slower rate was observed in the case of the di-NH-methane. An accurate difference could not be ascertained with the methods at our disposal but the difference could be qualitatively reproduced in a series of experiments.

The rate of chlorine consumption by the mono-N-methylmethane was studied in an analogous manner. Titration for chlorine after five seconds reaction time gave a blank in a series of experiments. The rate was thus too fast to measure by this technique.

The rate of bromination of the α -free pyrrole (III) has been measured by other workers⁹ in this Laboratory and found to be similar to that of the mono-N-methylmethane.

Behavior of Mono-N-methylmethane IV with Respect to Neutral and Alkaline Oxidation.—As mentioned in the theoretical part of this paper, many attempts were made to carry out the oxidation of the mono-N-methylmethane IV in neutral or basic medium using different reagents under different conditions. In order to test the applicability of the methods to general methene synthesis, every reaction was run on 3,5,3',5'-tetramethyl-4,4'-dicarbethoxydipyrrolylmethane (VI). All results on the mono-N-methylmethane (IV) were negative. The most interesting of the reagents tried was neutral permanganate which, when applied to the di-NH-methane, gives a good yield of very pure dipyrrolylmethene in the form of its free base. This method appears to be the best so far developed for preparing the free base of the di-NH-methene V in a high state of purity.

Oxidation of 3,5,3',5'-Tetramethyl-4,4'-dicarbethoxydipyrrolylmethane (VI) by Means of Potassium Permanganate.—The methane (150 mg.) was dissolved in 50 cc. of pure acetone in a 100-cc. Erlenmeyer flask fitted with a reflux condenser. (The acetone used in this reaction was obtained by refluxing commercial acetone for four hours over potassium permanganate.) 100 mg. of c. p. potassium permanganate was dissolved in the smallest amount of distilled water possible. The acetone solution was brought to a boil, the potassium permanganate solution added, and the mixture refluxed for five minutes. The reddish purple solution containing manganese dioxide was then filtered through asbestos; 125 mg. of the di-NH-methene (V) free base was obtained from the highly colored solution by rapid evaporation of the acetone. This material may then be recrystallized by dissolving in very little acetone, adding a small amount of water and allowing to stand overnight. It may also be recrystallized in the usual manner from hexane-benzene; m. p. (dec.) 190°.

The amount of potassium permanganate used in the above experiment was fixed by trial. The use of smaller amounts resulted in an impure product containing starting material; the use of larger amounts lowered the yield considerably. By following the pH of the reaction by means of a pH meter it was found that the pH rose rapidly to 13 and beyond when the methane solution and permanganate were mixed. By passing a stream of carbon dioxide through the reaction mixture, the pH could be maintained between 8 and 9. The reaction proceeded in this case much more slowly and considerably less permanganate was necessary. The product was of high purity but the yields were not so satisfactory as in the reaction just described. By using large excesses of permanganate and extending the reflux time, the methane was entirely converted to water soluble, colorless products.

When this technique was applied to the mono-N-methylmethane (IV) a white, crystalline product which was coated by a yellowish oil was obtained. On purification this product was found to consist largely of starting material.

Although many trials were made, no modification could be found whereby the expected methene could be prepared. Starting material was always obtained in decreasing

(9) Corwin and co-workers, unpublished work.

amounts with the use of large excesses of potassium permanganate. On the basis of work by Sackur and Taegen¹⁰ it was hoped that the use of a calculated amount of potassium permanganate in slightly alkaline solution would provide the methene. The results were disappointing since no reaction took place with increasing sodium hydroxide until a point was reached where the solvent itself was oxidized. In such cases the methane was completely destroyed.

Attempted Basic Bromination of Mono-N-methyldipyrromethane (IV).—A solution of 2.5 g. of potassium hydroxide dissolved in 100 cc. of methyl alcohol was cooled to -10° ; 2 g. of mono-N-methylmethane (IV) was dissolved in 200 cc. of carbon tetrachloride and placed in a 500-cc. three-necked flask equipped with a stirrer and dropping funnel. The methene solution was then cooled in a salt-ice mixture and stirring begun. The potassium hydroxide solution was poured into the flask and 0.9 g. of bromine dissolved in 25 cc. of carbon tetrachloride was added by means of the dropping funnel. After all the bromine solution had been added the stirring was continued for two hours. At the end of this time the solution had a bright yellow tinge. The solvent was evaporated off and water added to dissolve the potassium hydroxide. The yellowish residue after one crystallization proved to be the starting material; 2.25 g. was recovered. Warming the solution had no effect.

Formaldehyde Test on the Cleavage of the Mono-N-methyldipyrromethane in the Presence of Hydrobromic Acid.—The methane (500 mg.) was dissolved in 30 cc. of alcohol. To the solution 0.7 cc. of formaldehyde and 2 cc. of 45% hydrobromic acid were added. The solution was refluxed for one hour and the flask set aside to cool. The methane was precipitated by pouring the solution into cold water and filtering. The precipitate was dried and then refluxed with 66% alcohol. The mixture was filtered and the residue recrystallized from alcohol; yield, 425 mg. of beautifully white crystals; m. p. $178-179^{\circ}$ (irreversible); mixed melt with starting methane, $178-179^{\circ}$. The filtrate (66%) alcohol was evaporated down and a small precipitate obtained (50 mg.) which melted at $161-162^{\circ}$; mixed melt with starting methane $170-174^{\circ}$ (irreversible).

The same treatment was carried out in boiling carbon tetrachloride solution with the same results. It was assumed, therefore, that an appreciable cleavage of the methane under the influence of acid in boiling solvent does not take place.

Bromination of an Equimolar Mixture of the Di-NH-dipyrromethane (VI) and Di-N-methyldipyrromethane (VII).—The di-NH methane (VI) (250 mg.) is dissolved in 500 cc. of dry carbon tetrachloride by refluxing until the solution becomes clear. 275 mg. (1 mole) of di-N-methylmethane (VII) is then added. After the methane has completely dissolved, the solution is allowed to cool to room temperature and 0.16 g. of bromine dissolved in 1.6 cc. of dry carbon tetrachloride is run from a 10-cc. buret. The flask is then placed in an icebox overnight. The solution on filtering yields 380 mg. of red crystals covered with an appreciable amount of red oil. The crystals are treated with water which dissolves out the red oil (di-N-methylmethene). Weight of the dried crystals is 370 mg. or

85.4% of the theoretical based on one molar bromination of the di-NH-methene. The free base of the methene melts at 190° (dec.).

At the same dilution the yield of the di-NH-methene on half molar bromination of mono-N-methylmethane is 96%. The experiment shows that formation of these two methanes by cleavage of mono-N-methylmethane and recombination of the cleavage products to give a mixture of the two symmetrical methanes cannot account for the anomalous bromination of mono-N-methylmethane.

The apparent contradiction between the results of this experiment and those obtained from the preliminary rate studies, indicating a more rapid bromine consumption by the di-N-methylmethane than by the di-NH-methene may be explained by the greater stability and insolubility of the di-NH-methene. These factors tend to shift the equilibrium of the dipyrromethenes and their cleavage products in favor of the di-NH-methene.

Condensation of Mono-N-methyldipyrromethane (IV) with 2-Bromo-3,5-dimethyl-4-carbomethoxyppyrole (XV) (Reaction 5 Chart II).—The mono-N-methyldipyrromethane (360 mg.) is dissolved in 100 cc. of carbon tetrachloride. After cooling the solution to room temperature gaseous hydrogen bromide is passed in for one-half minute. A solution of α -bromopyrrole (XV) in carbon tetrachloride (250 mg. in 25 cc. of carbon tetrachloride) is run into the methane solution. After standing in the cold four hours, the solution on filtering yields 400 mg. of red crystals. The free base melts at 190° (dec.) and gives no depression with di-NH-methene (V); yield, 95%. Evaporation of the mother liquor yields N-methyl- α -free pyrrole.

Comparative Rates of Methene Formation in Mono-N-methyldipyrromethane- α -Bromopyrrole Condensation (Reaction 5) and Dipyrromethane Bromination.—A solution of 180 mg. of methane (IV) dissolved in 20 cc. of dry carbon tetrachloride (A) and a solution of 100 mg. of the methane (IV) in 15 cc. of dry carbon tetrachloride (B) were prepared in separate 50-cc. Erlenmeyer flasks. Dry, gaseous hydrogen bromide was then passed through each for thirty seconds. To solution A, 45 mg. of bromine dissolved in 0.5 cc. of carbon tetrachloride was added and the flask stoppered; 123 mg. of α -bromopyrrole (XV) in 5 cc. of carbon tetrachloride was then added to solution B. Each solution was allowed to stand for five minutes and then filtered. Solution A gave 70 mg. of the di-NH-methene (V) or 65% of the theoretical. Solution B yielded 165 mg. of methene (V) or 77% of the theoretical. Thus it could be shown that the condensation was a feasible reaction in the bromination.

Cleavage of 1,3,5,3',5',3'',5'''-Heptamethyl-4,4',4''-tricarboethoxytripyrromethane (XVI) by Hydrogen Bromide under the Conditions of the Bromination of the Mono-N-methyldipyrromethane (IV) (Reaction 6).—A solution of 100 mg. of the tripyrromethane (XIV) is prepared in a 50-cc. Erlenmeyer flask. Dry, gaseous hydrogen bromide is then passed through the solution for thirty seconds. After five minutes the solution is filtered; 75 mg. or 90% of the theoretical yield is obtained. Evaporation of the mother liquor yields N-methyl- α -free pyrrole (II).

Oxidation of Mono-N-methyldipyrromethane (IV) by 2-Dichloromethyl-4-methyl-3,5-dicarbomethoxyppyrole.—A solution of 180 mg. of the methane (IV) in 5 cc. of rectified

¹⁰ Sackur and Taegen, *Z. Elektrochem.*, **18**, 718 (1912).

dioxane is prepared in a 25-cc. Erlenmeyer flask. To this solution is added 160 mg. of the dichloromethylpyrrole dissolved in 5 cc. of rectified dioxane. Dry gaseous hydrogen chloride is then passed in until the solution is saturated and the stoppered flask allowed to stand in the cold for several days; 35 mg. of deep red needles is obtained. Tests described above show the product to be the di-NH-methene (V); m. p. (dec.) of the free base 190°.

Bromination of 3,5,4'-Trimethyl-4,3',5'-tricarbethoxydipyrrolymethane (XVII).—The dipyrrolymethane (XVII) (500 mg.) is dissolved in 500 cc. of dry carbon tetrachloride; 0.2 g. of bromine dissolved in 5 cc. of carbon tetrachloride is added to this solution at room temperature. After standing for several hours 500 mg. of fine red needles is filtered from the mixture. On conversion to the free base, by treatment of the solid methene salt with dilute ammonium hydroxide, this compound is shown to be identical with the unsymmetrical 3,5,4'-trimethyl-4,3',5'-tricarbethoxydipyrrolymethane (XVIII), synthesized by independent methods; m. p. of free base 125° (dec.); yield 83%.

Bromination of 1,4,3',5'-Tetramethyl-3,5,4'-tricarbethoxydipyrrolymethane (XIX).—The mono-N-methylmethane (XIX) (0.5 g.) is dissolved in 500 cc. of dry carbon tetrachloride; 0.2 g. of bromine dissolved in 5 cc. of carbon tetrachloride is added quickly to this solution with stirring. The dark red solution is allowed to stand in the cold overnight. On filtration 100 mg. of fine yellow-red needles is obtained. In addition, a large amount of red oil is found on the walls of the flask. No identifiable products have been obtained from this residue. Tests described above showed the red crystals to be the symmetrical di-NH-methene (V).

Summary

1. The oxidation of the leuco base of an unsymmetrical pyrrole pigment to a symmetrical pyrrole pigment having the sequence of substituents which corresponds to one of the pyrrole rings in the base has been observed.
2. This anomalous reaction has been shown to result from a reshuffling of intact pyrrole rings rather than by attack on the pyrrole substituents.
3. The application of this reaction to the study of the regrouping of pyrrole rings in naturally occurring pyrrole pigments is suggested by the mild conditions under which the reaction takes place.
4. The transformation has been shown to involve a cleavage of a carbon-carbon bond in the aromatic system of an intermediate in the reaction.
5. Two similar mechanisms have been proposed and supported by experimental evidence.
6. The oxidation of a number of unsymmetrical dipyrrolymethanes has been studied to test the generality of the anomalous reaction. Another example has been found.

BALTIMORE, MARYLAND

RECEIVED MAY 28, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Preparation and Dehydration of 6-Methoxy-*i*-norcholenyldiphenylcarbinol

BY BYRON RIEGEL, MELVIN F. W. DUNKER¹ AND McCALIP J. THOMAS²

For the systematic degradation of the side chain of methyl 3-hydroxy-5-cholenate (I), an investigation involving the use of the so-called *i*-methyl ether, primarily to protect the hydroxyl group and the double bond, has been made. The dehydration of the carbinol, resulting from the reaction with the Grignard reagent, proved to be a critical reaction provided the *i*-ether structure is retained. Hence, this reaction was studied.

Methyl 3-*p*-toluenesulfonyloxy-5-cholenate (II)³ was converted to methyl 6(α)-methoxy-*i*-cholenate (III) by the usual method, namely, by heating a methanol solution containing anhydrous potassium acetate. The reaction of this *i*-methyl

ether methyl ester (III) with phenylmagnesium bromide gave the desired 6(α)-methoxy-*i*-norcholenyldiphenylcarbinol (IV) which melted at 139.0–140.2° and gave a specific rotation of +43.9°. Carbinol (IV) could not be dehydrated in a solution of boiling glacial acetic acid without changing the *i*-methyl ether structure to the normal acetate, thus giving 3-acetoxy-24,24-diphenyl-5,23-choladiene (VII). Even heating a glacial acetic acid solution of carbinol (IV) for a short time caused dehydration with a simultaneous loss of the *i*-ether configuration. Because of the lability of the *i*-steroid structure, particularly toward acidic reagents, many dehydrating agents cannot be used if this structure is to be retained. Although Heilbron, Beynon and Spring⁴ had dem-

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