

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

The Determination of the Bridge Structure of Dipyrrolymethanes. A New Method for the Estimation of Active Hydrogen¹

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The preceding paper of this series³ showed that the imide hydrogens of certain dipyrrolymethanes do not react with molten sodium and potassium. Conceivably, these peculiarities could be due to the absence of imide hydrogens as a result of N-C-N bridges instead of C-C-C bridges as usually formulated. A suitable tool for the investigation of this problem would be a method for the determination of active hydrogens which would permit a demonstration that no rearrangement of the carbon-nitrogen skeleton had taken place during the course of the determination. This could be accomplished by regeneration of the original compound if an active hydrogen reagent could be found which would not alter ester or carbonyl groups.

A convenient reagent which has the properties specified above was suggested by the work of Conant and Wheland⁴ and that of McEwen.⁵ The method involves the titration of a solution of the compound in question with a standardized solution of sodium triphenylmethyl, using the color of the reagent as the end-point indicator. This reagent has the added advantage that it provides a convenient means for the preparation of derivatives, for example, methyl homologs, by reaction with the sodium salt formed during the titration.

To learn whether or not sodium triphenylmethyl is a specific reagent for imide hydrogens, this new method was used on various simple pyrroles. The results of this survey are summarized in Table I.

Perusal of the table establishes the following facts: sodium triphenylmethyl is unreactive toward nuclear methyl groups, carbethoxy groups, bromine or hydrogen on carbon; it is reactive toward imide hydrogens and hydroxyl groups. It is interesting to note that compound V, which is inert to sodium, reacts with this reagent. Compound VII shows more than one active hydrogen

TABLE I
ACTIVE HYDROGEN DETERMINATION ON SIMPLE PYRROLES

Pyrrole	Chemical Structure	Active H
I		0.0 .0
II		1.13 0.98 .99
III		.0 .0
IV		1.07 1.03 1.17
V		1.00
VI		0.98 .97
VII		> 1.0
VIII		1.94
IX		1.04

and on titration no sharp end-point could be reached. Up to the first mole the color of the reagent disappeared immediately. After that point had been passed, there was a slow fading of the color after each addition of the reagent. McEwen⁴ has shown that the *pK* value of acetophenone is about 19 while that of triphenylmethane is approximately 33. By analogy, the *pK* value of the eno form of this acetyl pyrrole should be near to that of acetophenone and the

(1) Studies in the Pyrrole Series. IX. This paper is from the doctoral dissertation of Rudolph C. Ellingson, The Johns Hopkins University, 1938, and was presented at the Baltimore Meeting of the American Chemical Society, April, 1939.

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(3) Corwin, Bailey and Viehl, *THIS JOURNAL*, **64**, 1207 (1942).

(4) Conant and Wheland, *ibid.*, **54**, 1212 (1932).

(5) McEwen, *ibid.*, **58**, 1124 (1936).

slowly fading color may be ascribed to slow formation of the enol catalyzed by the strong base used.

The sodium salt of pyrrole II, formed during the titration, can be converted to compound I by reaction with dimethyl sulfate. In the same manner, the mono- and di-N-methyl derivatives of 3,5,3',5'-tetracarboxy-4,4'-dimethyldipyrromethane (X, Table II) may be prepared by successive alkylations after the formation of sodium salts by the sodium triphenylmethyl. This duplicates the reaction series described by Corwin, Bailey and Viohl.³ In every case the sodium salts were hydrolyzed with water and the starting dipyrromethanes were recovered unchanged by the reagent.

The final methane in this methylation series, methane XII, Table II, exhibits peculiarities under the conditions of the reaction. On treatment with sodium triphenylmethyl, the end-point color appears as soon as the amount of reagent equivalent to the solvent blank has been added. When one mole of reagent is added, a flocculent orange precipitate settles out. Treatment of this solution with water regenerates the starting dipyrromethane. Attempts to methylate the precipitate with dimethyl sulfate failed and in each case starting material and triphenylmethane were isolated. The isolation of triphenylmethane shows that the orange precipitate is not sodium triphenylmethyl because methylation of this substance gives 1,1,1-triphenylethane.

We interpret the peculiarities noted by the assumption that one of the bridge hydrogens of the di-N-methylmethane is sufficiently acidic to react with sodium triphenylmethyl but that the steric relations of the sodium salt formed make methylation difficult.⁶ The color obtained upon addition of sodium triphenylmethyl, according to this explanation, would be that of the substituted dipyrromethyl ion. From the broadest point of view, such a reaction as this constitutes a limitation to the method which we use. Actually, however, since the N-sodium salts are colorless, the formation of the colored C-sodium salt does not interfere with the determination of active imide hydrogens.

A variety of dipyrromethanes was studied with this reagent. The summary of the titrations is given in Table II.

It should be noted that methane XVII, which was inert to sodium,³ shows two active hydrogens

with sodium triphenylmethyl and that the titration values on compound XX confirm the inertness of a pyrrol CH toward this reagent.

The disodium salt of compound XIII, obtained by this titration, methylates nicely at room temperature to give 1,3,5,1',3',5'-hexamethyl-4,4'-dicarboxy-dipyrromethane (XXI). The compound prepared by this method shows no melting point depression with that obtained by the condensation of 1,2,4-trimethyl-3-carboxypyrrole with formaldehyde.⁷

On treating compound XIII with one mole of sodium triphenylmethyl and subsequently methylating, one obtains a mixture of the mono- and di-N-methyldipyrromethanes (XIV and XXI) which can be separated by fractional crystallization since the mono-N-methylmethane is the less soluble in alcohol. Methane XIV, after titration, can be methylated in good yield to give methane XXI. In each case the sodium salts were hydrolyzed to the original compound to make certain that no condensation or cleavage was caused by sodium triphenylmethyl.

The possibility that methane XIII might be N-C-N and show active hydrogens due to an active bridge CH group was eliminated by comparing compound XIV with methane XV obtained by the condensation of 2,4-dimethyl-3-carboxypyrrole with acetaldehyde.⁸ Although these two substances melt only four degrees apart, mixed melting point shows a marked depression.

Mixed melting points of two of the three possible combinations of methanes XIII, XIV and XXI show depressions; the mixture of XIII and XIV shows no definite depression, however. In spite of this, the evidence is overwhelming that compound XIV is one pure compound. Its analysis agrees well with the calculated values and the possibility of its being an equimolar mixture of XIII and XXI was eliminated by comparison with such a mixture prepared artificially: the artificial mixture melts at 148-150° and its mixed melting point with the methane XIV depresses to 141-142°. Finally, such a mixture can be separated into its components by crystallization while repeated recrystallizations of compound XIV fail to effect any separation.

The several lines of evidence summarized above establish the bridge structure of methane XIII and its methyl derivatives as C-C-C and illus-

(7) Corwin and Quattlebaum, *ibid.*, **58**, 1085 (1936).

(8) Fischer and Bartholomäus, *Z. physiol. Chem.*, **87**, 264 (1913).

(6) See Brunings and Corwin, *THIS JOURNAL*, **64**, 593 (1942).

Dipyrrylmethane		Solvent	Active H
X		Benzene	1.72, 1.82 ^a
XI		Benzene Dioxane	0.96, 0.96, 1.04 1.06, 1.11, 1.13
XII		Benzene	0.0
XIII		Dioxane	2.12, 2.19
XIV		Dioxane	1.01
XV		Dioxane	1.88
XVI		Dioxane	2.10
XVII		Benzene Dioxane	1.95, 1.97 2.08, 2.00, 2.03
XVIII		Dioxane	1.08, 1.09
XIX		Benzene	2.02, 2.08
XX		Dioxane	1.96, 2.10
XXI		Benzene	0.0

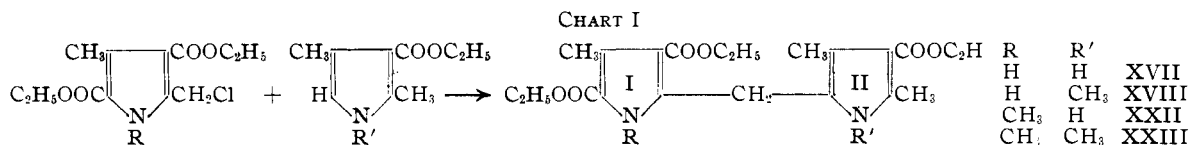
^a The low values for this compound are undoubtedly due to the use of benzene as a solvent since the mono-sodium salt was later found to precipitate out of the benzene. Our later procedure was to use dioxane as solvent in such cases.

trate the use of the combined titration and methylation technique in a structural investigation.

The study of methane XVII and its methylation products, besides providing proof of its bridge

structure, furnishes illustrations of the specificity which may be obtained by the control of reaction conditions and of an unexpected limitation to the method of titration with sodium triphenylmethyl.

Methane XVII was synthesized by application of the following general method



in which both R and R' were H. Its melting point is 158°.

Reaction of this compound with one mole of sodium triphenylmethyl should give a mono-sodium salt by replacement of the more acidic hydrogen, which, because of the electron-attracting influence of the carboxy groups, would be predicted to be that on ring I. Methylation gives a mono-N-methylmethane XXII; m. p. 113°, identical with that prepared by Quattlebaum and Corwin⁹ by the method of Chart I in which R is CH₃ and R' is H. This confirms the prediction as to the relative acidities of rings I and II.

Since the imide hydrogen of ring II is less acidic than that of ring I, its sodium salt will be a stronger base than the sodium salt of ring I, and methylation of the disodium salt should take place most rapidly on ring II as a consequence of the greater availability of electrons at this point. This course of the reaction is that found by experiment. Compound XVIII is formed by monomethylation of the disodium salt. The structure is confirmed by the reaction of Chart I in which R is H and R' is CH₃. Thus either ring may be selected for specific methylation.

The low solubility of the sodium salt of methane XVIII prevents ready methylation at room temperature. If, however, the disodium salt of XVII is refluxed with two moles of dimethyl sulfate or the monosodium salt of XVIII is refluxed with one mole of dimethyl sulfate, complete N-methylation is accomplished. The structure of the product XXIII melting at 129°, was confirmed by the reaction of Chart I.

When methane XXII was treated in dioxane solution with sodium triphenylmethyl, an intense red-violet color with a blue fluorescence appeared long before one mole of reagent per mole of methane had been added.³ There was no appreciable precipitate in this solution. Hydrolysis of the solution with water or treatment with dimethyl sulfate gave the same compound in the form of yellow plates melting at 204°. Analysis of the

product indicates that a condensation has taken place. The further investigation of the structure

of this substance will be the subject of a later communication.

When methane XXII is treated with sodium triphenylmethyl in benzene solution, in which sodium salts are generally much less soluble than in dioxane, a colorless, soap-like precipitate is formed and indications of the condensation reaction appear when nearly one mole of reagent per mole of methane has been added. The violet color and blue fluorescence make it impossible to determine the end-point visually and therefore we cannot titrate accurately for the number of active hydrogens in the molecule. If the solution with its precipitate is immediately treated with water, the sodium salt is hydrolyzed and one obtains an 85% recovery of the starting mono-N-methylmethane XXII. If the solution is treated immediately with dimethyl sulfate, a 60% yield of methane XXIII is obtained.

The anomaly recorded above, while illustrating a limitation of the sodium triphenylmethyl titration, emphasizes one of the advantages of the reagent, namely, that the possibility of regeneration of the starting compound permits a check upon the presence or absence of an undesired side-reaction and thus furnishes a more reliable means for the investigation of structure than the usual active hydrogen determination.

The authors wish to acknowledge their deep indebtedness to Dr. F. Y. Wiselogle for his generous aid and consultation in the manipulation of sodium triphenylmethyl.

Experimental Part

Purification of Nitrogen.—In using standardized solutions of sodium triphenylmethyl, it is necessary to prepare and manipulate the compound under nitrogen that has been freed from carbon dioxide, moisture and oxygen. A convenient purification train is shown in Fig. 1.

Tank nitrogen is passed through a series of six Friedrich's spiral wash bottles. The first two contain 150 cc. each of Fieser's solution.¹⁰ This solution is very effective for removing oxygen. When the first bottle has become exhausted, as evidenced by the change in color, it is refilled with fresh solution and placed in position 2, while bottle 2

(9) Quattlebaum and Corwin, *THIS JOURNAL*, **64**, 922 (1942).

(10) Fieser, *ibid.*, **46**, 2639 (1924).

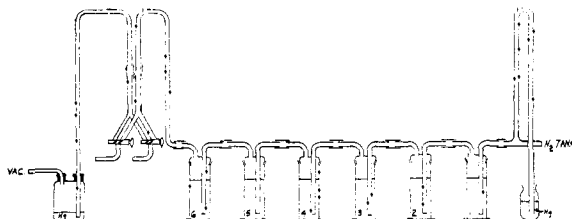


Fig. 1.

is placed in the first position. The third wash bottle contains a saturated lead acetate solution to remove any hydrogen sulfide that may be liberated from the Fieser's solution; in the fourth bottle there is concentrated sulfuric acid to remove water; in the fifth a deep blue toluene solution of the sodium ketyl of benzophenone prepared by dissolving a few grams of benzophenone in dry toluene and adding a small amount of 2% sodium amalgam. This solution removes the last traces of water and oxygen and serves as an indicator for the purity of the nitrogen. The sixth wash bottle contains Nujol in which paraffin has been dissolved to catch the toluene vapors swept from the benzophenone bottle. The train is so constructed that nitrogen can be led to two systems and so arranged that each can be evacuated and filled with nitrogen as many times as necessary, independently of the other. The ground joints of the wash bottles are secured with paraffin during operation.

Preparation of Sodium Triphenylmethyl Solution.—The apparatus in which the sodium triphenylmethyl is prepared

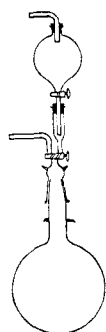


Fig. 2.

consists of a 500-cc. round-bottom flask with a ground joint connection to a filling and sweeping apparatus as shown in Fig. 2. We are indebted to Dr. F. Y. Wiselogle for the design of this apparatus.

The solvents, benzene and ether, are carefully dried over 45% sodium amalgam, distilled and distilled again from 2% sodium amalgam and benzophenone immediately before being used. The blue color of the metal ketyl indicates when the solvents are absolutely dry. The stopcocks and ground joints are lubricated with a lubricant reported by Meloche and Frederick.¹¹ All parts are baked at 110° for several hours before being used.

In the flask is placed 100 cc. of dry ether and about 20 g. (9–10 cc.) of 45% sodium amalgam is added. In the separatory funnel a solution of 12 g. of pure triphenylmethyl chloride in 100 cc. of dry benzene is placed. The two parts are evacuated and filled with nitrogen three or four times to replace the air. The benzene solution is then run into the flask below. The stopcock is turned so that the lower part is connected to the nitrogen current and the flask shaken for about one-half hour. The flask is left on the nitrogen current to take care of the pressure built up due to vaporization of ether. The stopcock is closed, the separatory funnel removed and the flask placed on a shaking wheel for twelve to fourteen hours.

The sodium triphenylmethyl solution is filtered from sodium chloride and mercury through a 3G4 sintered glass funnel into the storage vessel which is a one liter flask with

a delivery tube and inlet neck, each carrying ground glass stopcocks (Fig. 3). On the side arm of the reaction vessel is placed a rubber stopper which fits into the top of the sintered glass funnel and the stem of this has a rubber stopper fitting into the inlet neck of the storage vessel.

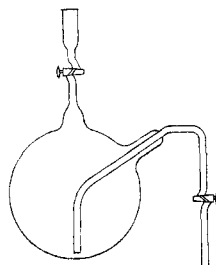


Fig. 3.

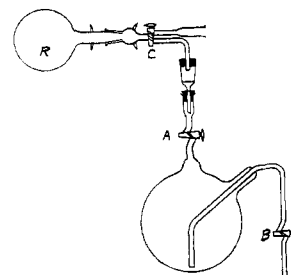


Fig. 4.

The reaction flask and storage vessel are placed in the tilted position (Fig. 4) ready for filtration but are allowed to stand for three or four hours so the finely divided salt, mercury and sodium amalgam have time to settle. This is important or the sintered glass funnel will become stopped up immediately. After the settling, the stopcocks A and B are opened and the vessel evacuated and filled with nitrogen three times; finally stopcock A is closed, the vessel evacuated and the stopcock B is closed. Stopcock C is opened and after the glass funnel has liquid over the bottom, A is opened. The whole apparatus is tilted so liquid always fills the neck of the reaction vessel, R. The filtering proceeds rapidly at first but slows considerably toward the end. After filtering, stopcock A is closed and B opened allowing nitrogen to enter, relieving the vacuum.

The separatory funnel is placed in the neck of the storage vessel and a mixture of 125 cc. of dry ether and 125 cc. of dry benzene is run in. The solution is shaken and is then ready for use. In this way a sodium triphenylmethyl solution of 0.07 to 0.08 molarity is obtained and can be kept for weeks with very little change in strength.

Apparatus for the Titrations.—The apparatus for the titrations is shown in Fig. 5. The storage vessel is mounted high on a ring stand. A tube about four inches long and drawn out at one end is attached to the delivery tube of the vessel by a slip-over rubber seal making the union nearly glass to glass. The narrow end leads into the top of a 10-cc. buret and is also sealed by a slip-over rubber tube. The buret has a side arm about half an inch above the zero mark and is connected to the nitrogen purification train.

The most satisfactory stopcock grease for the buret is graphite and tin amalgam. The two parts of the stopcock are well coated with graphite by rubbing with an extra soft lead pencil and then with a piece of tin that has been dipped in mercury. This lubricant holds the ether-benzene solution very well and will hold a water-pump vacuum quite well. The stopcock does not freeze and may be used several days without relubricating.

The end of the buret carries a rubber stopper that fits into the neck of the reaction flask which is a 50-cc. suction flask to which an "L" side arm has been added. The regular side arm is connected to the purification train while the "L" arm is used for introducing the solvent and the methylating agent.

(11) Meloche and Frederick, *THIS JOURNAL*, **54**, 3264 (1932).

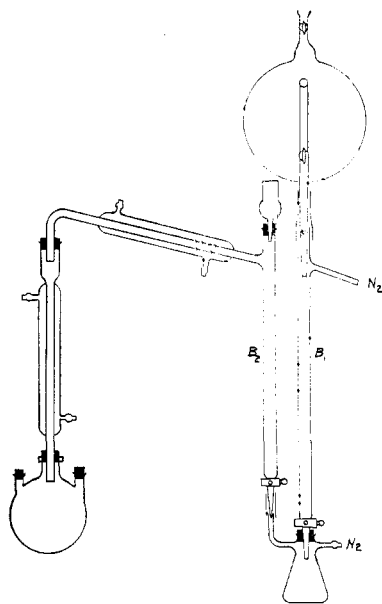


Fig. 5.

The solvent, dioxane or benzene, is refluxed in the flask over 2% sodium amalgam and benzophenone until dry as indicated by the blue color. It is then distilled into the buret, B_2 , from which the solvent is measured directly into the reaction vessel. The tip of B_2 fits into the "L" arm of the reaction flask and is sealed with a slip-over rubber tube.

Another reaction vessel was constructed from a 50-cc. suction flask with the "L" side arm and a two-inch glass condenser (Fig. 6). This was used when methylation did not take place at room temperature but required heat. The flask was heated by a small electric furnace.

Directions for Performing a Titration. A. Standardization of Sodium Triphenylmethyl Solution.—The buret is evacuated and filled with nitrogen three times and finally evacuated. Stopcock B of the storage vessel is opened so that a few cc. of solution runs into the buret. B is closed and nitrogen again led into the buret. This amount of reagent is run out and discarded, serving merely to remove any water that may not have been removed on cleaning and drying the buret. The buret is then filled and a definite volume of the solution run into a 50-cc. Erlenmeyer flask containing 20 cc. of distilled water. This flask is heated on a steam-bath to remove the solvents, ether and benzene, cooled and the solution titrated with standard hydrochloric acid using methyl orange as the indicator. Duplicate titrations are run and from these the strength of the reagent solution is calculated.

B. Blanks on the Solvent.—The reaction flasks are dried at 110° to remove all moisture. The empty flask is attached, evacuated and sealed with paraffin at the stopper and rubber slip-over seals while under vacuum. Nitrogen is then allowed to pass in and the evacuation and refilling repeated three times. The flask is evacuated slightly and 5 cc. of solvent measured in from buret B_2 and the stopcock turned to the nitrogen current again. In the meantime the reagent buret has been filled as described earlier. The reagent is then added dropwise, the flask being shaken gently until the permanent orange color

appears in the solvent. Duplicates also are performed for this step. For 5 cc. of benzene the blank is 0.22 to 0.26 cc. when the strength of the reagent is 0.07 to 0.08 molar. For 5 cc. of dioxane it is 0.80 to 1.00 cc. for the same strength of reagent. Dioxane that is used as a solvent is purified by storing over calcium chloride for several days, refluxing over sodium for several hours, distilling, and finally distilling from 2% sodium amalgam and benzophenone in the titration apparatus.

C. Titration of the Sample and Methylation.—The pure, dry sample is weighed into the reaction flask and attached to the apparatus. The solvent is introduced as described above for the blank determinations and the reagent buret filled. The reagent is added slowly to the permanent end-point. The number of active hydrogen atoms per molecule of the compound can then be calculated.

If one wishes to hydrolyze the reaction product to see whether or not the starting material will be recovered, the flask is removed, the product treated with water and the material worked up as will be described in the individual experiments.

If one wishes to methylate the reaction product, the solution of dimethyl sulfate is passed into buret B_2 , the reaction flask is evacuated slightly and as much of this solution is added as desired. Since the molar quantities used are very small, 1 cc. of dimethyl sulfate is made up to 10 cc. with dry solvent used in the titration to allow a more accurate measurement of the amount of methylating agent. The dimethyl sulfate is also distilled through a small column under vacuum just before being used. For those methylations where heat must be applied the reaction vessel shown in Fig. 6 is used.

Titrations were performed by this method on all the substances listed in Tables I and II with the results shown.

In the succeeding section only experiments other than the titrations are described.

1,2,4-Trimethyl-3,5-dicarbethoxypyrrole (I).—2,4-Dimethyl-3,5-dicarbethoxypyrrole (II), (146 mg.) was titrated as described above. The sodium salt formed was methylated by adding 3.5 cc. of dimethyl sulfate. After standing two hours the solution was filtered, the solvent removed and excess dimethyl sulfate destroyed by steam distillation; yield, 110 mg. or 71% of colorless crystals; m. p. $109-111^\circ$. The compound gives no melting point depression with a pure sample of the N-methylpyrrole.

Activity of the Reagent toward Nuclear Methyl and Carbethoxy Groups.—To make certain that no reaction had taken place with nuclear methyl and carbethoxy groups, compounds I and III were recovered after the titration by evaporation of the solvent and compound II by hydrolysis of the solution. None showed any depression on mixed melting point with the starting material.

Reactions with 3,5,3',5'-Tetracarbethoxy-4,4'-dimethyldipyrromethane (X). **A. Recovery after Titration.**—The tetracarbethoxymethane (212 mg.) was titrated in benzene solution. The reaction mixture was shaken with water, the benzene layer separated, dried over sodium sulfate, filtered and evaporated. The residue was extracted with

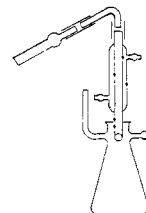


Fig. 6.

hexane to remove the triphenylmethane. The crude material (133 mg. or 63%) was crystallized from ethanol; m. p. 134–135°, no depression of m. p. with starting material.

B. Monomethylation.—Two hundred and twenty-eight milligrams of methane X was treated with 11.70 cc. (including 0.40 cc. solvent blank) of 0.0445 molar sodium triphenylmethyl solution. 2.00 cc. of dimethyl sulfate was added and the solution warmed for ninety minutes. The solution was filtered and the solvents removed by steam distillation. The insoluble solid was dried and extracted with 5 cc. of hot hexane to remove the triphenylmethane; yield, 133 mg. or 56%. After recrystallization from alcohol and water the m. p. was 139–140°. There was no depression with compound XI prepared with sodium and dimethyl sulfate but there were marked depressions with methanes X and XII.

C. Dimethylation.—One hundred and ninety-nine milligrams of methane X was treated with 20.19 cc. (including 0.40 cc. solvent blank) of 0.0445 molar sodium triphenylmethyl solution; 3.00 cc. of dimethyl sulfate was added and the solution warmed for ten minutes. The solvents were removed by steam-distillation. The residue was dried and extracted with hexane to remove triphenylmethane; yield, 186 mg. or 91% of the di-N-methylmethane XII.

Reactions with 1,4,4'-Trimethyl-3,5,3',5'-tetracarboethoxydipyrrylmethane (XI). **A. Recovery after Titration.**—The procedure was identical with that described for methane X; no depression with starting material.

B. Methylation.—The procedure was identical with that for the monomethylation of compound X with the proper correction for the change in molecular weight; yield, 70–90%. No depression with methane XII.

Reaction with 1,4,1',4'-Tetramethyl-3,5,3',5'-tetracarboethoxydipyrrylmethane (XII). **A. Treatment with One Mole of Reagent and Hydrolysis.**—Three hundred and seven milligrams (0.000635 mole) of the dipyrrylmethane XII in 5 cc. of benzene was treated with enough reagent solution to furnish 0.00064 mole of sodium triphenylmethyl. The permanent end-point appeared as soon as enough solution for the blank had been added. As the addition proceeded a deep red, transient precipitate formed as the drops hit the surface. By the time one mole of reagent had been added there was an orange-yellow substance suspended in the red solution. This solution was treated with water and the product isolated in the usual manner, giving 175 mg. of a colorless solid which after two crystallizations from alcohol melted at 144–145° and did not show a depression with the starting methane.

B. Attempted Methylations.—Two hundred and fifty-six milligrams (0.00053 mole) of methane XII in 5 cc. of benzene was treated with 0.00053 mole of sodium triphenylmethyl; 1 cc. of dimethyl sulfate was added and the solution allowed to stand several hours. It was then shaken with an 8% sodium carbonate solution, washed with water, dried, filtered and evaporated. The residue was extracted with hexane leaving 125 mg. of colorless material which melted at 141–143° and did not depress on mixed m. p. with the starting methane.

The experiment was repeated using 265 mg. of the methane and twice the amount of sodium triphenyl-

methyl; 85 mg. of material was isolated which proved to be the starting methane.

Two hundred and nineteen milligrams (0.00045 mole) of the dipyrrylmethane in 5 cc. of benzene was treated with 0.00045 mole of sodium triphenylmethyl and 0.0011 mole of dimethyl sulfate and allowed to stand for twelve hours. The solution was filtered and evaporated in vacuum. The residue was boiled with hexane, filtered, and 42 mg. of a pink solid that melted at 92–96° was isolated. The hexane filtrate was evaporated down leaving 200 mg. of residue which was crystallized from alcohol and water; m. p. 87–90°. It showed no depression on mixed melt with triphenylmethane but gave a 30° depression with 1,1,1-triphenylethane. This demonstrated that sodium triphenylmethyl was not present in the solution after treatment with methane XII.

Reactions with 3,5,3',5'-Tetramethyl-4,4'-dicarboethoxydipyrrylmethane (XIII). **A. Recovery after Titration.**—The procedure was identical with preceding recoveries; 53 mg. was obtained from 98 mg. and was identical with the starting material.

B. Monomethylation.—Four hundred and thirteen milligrams (0.0012 mole) of methane XIII was dissolved in 10 cc. of dioxane and treated with 0.0012 mole of sodium triphenylmethyl; 1.0 cc. of dimethyl sulfate was added and the sodium salt went into solution rapidly leaving a small amount of sodium methyl sulfate suspended. The solution was washed with water, the benzene-ether layer separated, dried over sodium sulfate, filtered, evaporated and the residue extracted with hexane, leaving 450 mg. of a tan powder. The powder was boiled with 30 cc. of 2:1 alcohol-water and filtered, leaving 290 mg. of undissolved material melting at 150–160°. This was crystallized several times from alcohol and water; m. p. 176° with decomposition. The compound crystallized in colorless plates and depressed with di-N-methylmethane XXI. Mixed m. p. with the starting material (XIII), m. p. 229°, was 178–179° thus showing no definite depression. The filtrate from the first crystallization gave, on cooling, 85 mg. of impure di-N-methylmethane XXI.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$ (methane XIV): C, 66.65; H, 7.83. Found: C, 66.58; H, 7.79.

C. Dimethylation.—Three hundred and fifty milligrams (0.00101 mole) of methane XIII in 10 cc. of dioxane was treated with 0.0020 mole of sodium triphenylmethyl; 1.0 cc. of dimethyl sulfate was added and the solution allowed to stand for several hours. It was then treated in the same manner as for the monomethylation; 255 mg. or 67% of crude di-N-methyl methane XXI was isolated. After five recrystallizations from alcohol and water its melting point rose to 150–152° and showed no depression on mixed melt with a sample prepared by the method of Corwin and Quattlebaum.⁷

Methylation of 1,3,5,3',5'-Pentamethyl-4,4'-dicarboethoxydipyrrylmethane (XIV).—After titration in 5 cc. of dioxane, the sodium salt from 123 mg. of methane XIV was treated with 0.0007 mole of dimethyl sulfate and warmed gently. After standing for several hours the solution was shaken with water, the benzene-ether layer separated, dried over sodium sulfate, filtered and evaporated in a vacuum. The residue was extracted with 5 cc. of warm hexane; yield, 78 mg. or 61%; m. p. 153°. The melting

point was raised to 157–158° by repeated recrystallizations from alcohol and water. No depression with methane XXI, m. p. 153°, prepared by the method of Corwin and Quattlebaum.⁷

Comparison of Methane XIV with XV.—The bridge methylated methane XV was prepared by the method of Fischer and Bartholomäus.⁸ After recrystallization from alcohol and water the melting point was 170°. The melting point of methane XIV was 176°; mixed m. p. 153°.

Reactions of 3,5,4'-Trimethyl-4,3',5'-tricarbethoxydipyrromethane (XVII). **A. Recovery after Titration.**—The solution obtained by titrating 174 mg. of methane XVII was poured into 50 cc. of water, heated on the steam-cone to remove the ether and benzene, cooled and the solid filtered off. This solid was boiled with hexane, the solution cooled and filtered; recovery, 163 mg. or 94% of crude starting material. After one crystallization from alcohol and water the compound melted at 156–158° and gave no depression with starting material, m. p. 158–159°.

B. Monomethylation of XVII on Ring I.—Two hundred and four milligrams (0.000505 mole) of methane XVII was dissolved in 5 cc. of dioxane and treated with 0.00051 mole of sodium triphenylmethyl. To the clear solution, 0.9 cc. of a 10% solution by volume of dimethyl sulfate and benzene was added and the reaction mixture allowed to stand overnight; 50 cc. of water was added and the mixture heated on the steam-cone to remove the ether and benzene, cooled, the solid removed and dried. The solid was extracted with cold hexane; yield, 153 mg. (72%) of a colorless powder; m. p. 105°. After two crystallizations from water and alcohol, m. p. 110°; mixed m. p. with methane XXII prepared by the method of Quattlebaum and Corwin,⁹ no depression.

C. Monomethylation of XVII on Ring II.—Two hundred and two milligrams of methane XVII (0.00050 mole) was dissolved in 5 cc. of dioxane and 0.00104 mole of sodium triphenylmethyl beyond the solvent blank was added. The sodium salt came out as a gelatinous mass; 1.8 cc. of dimethyl sulfate solution (1 cc. in 9 cc. of dioxane) was added. Within two minutes the solution had become apparently clear and within the next few seconds a large amount of a white precipitate separated—much more than the sodium methyl sulfate could account for. The flask was allowed to stand attached to the apparatus overnight; 40 cc. of water was added, the mixture heated on the steam-cone to remove the solvents, cooled and the solid separated and dried. The solid was boiled with 3.0 cc. of hexane, the solution cooled, filtered and the residue washed with cold hexane; yield, 145 mg. or 68%; m. p., after one crystallization from alcohol and water, 96°. Repeated crystallizations raised this to 97°; no depression with methane XVIII prepared by the method given below.

D. Synthesis of 1,3,5,4'-Tetramethyl-4,3',5'-tricarbethoxydipyrromethane (XVIII) by Condensation.—Two and seventy-three hundredths grams of 2-chloromethyl-3,5-dicarbethoxy-4-methylpyrrole was dissolved in 10 cc. of methanol and 1.81 g. of 1,2,4-trimethyl-3-carbethoxy-pyrrole in 5 cc. of methanol. The solutions were combined and refluxed two hours. The reaction mixture was cooled until crystallization was complete and the solid filtered off; yield, 2.60 g. or 62%; m. p. 92–94°. No attempt was made to recover the product in the mother liquors from the

condensation; m. p., after one crystallization from water and alcohol, 96–97°. For analysis, crystallized twice from hexane; m. p. 97°.

Anal. Calcd. for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.22. Found: C, 63.08; H, 7.26.

E. Dimethylation of Methane XVII.—One hundred and five milligrams (0.00026 mole) of methane XVII in 5.0 cc. of benzene was treated with 0.000556 mole of sodium triphenylmethyl; 3.0 cc. of dimethyl sulfate solution (1 cc. in 9 cc. benzene) was added and the solution refluxed for forty minutes. The sodium salt dissolved and deposited sodium methyl sulfate; 50 cc. of water was added, the solution heated to remove the benzene and ether, cooled and filtered. The solid was extracted with hexane; yield, 85 mg. or 75%; m. p. 125°; after crystallizing from hexane, m. p. 128–129°; no depression with methane XXIII prepared by the condensation below.

F. Synthesis of 1,3,5,1',4'-Pentamethyl-4,3',5'-tricarbethoxydipyrromethane (XXIII) by Condensation.—Two and eighty-seven hundredths grams of 1,4-dimethyl-2-chloromethyl-3,5-dicarbethoxy-pyrrole and 1.81 g. of 1,2,4-trimethyl-3-carbethoxy-pyrrole were each dissolved in 5 cc. of methanol. The solutions were combined and refluxed for two hours. On cooling the dipyrromethane crystallized out; yield 3.85 g. or 89%; m. p. 128–129°. The analytical sample was crystallized twice from alcohol and water and once from hexane; m. p. 129°.

Anal. Calcd. for $C_{28}H_{32}N_2O_6$: C, 63.87; H, 7.46. Found: C, 63.88, 63.80; H, 7.46, 7.38.

Reactions for Methane XVIII. **A. Recovery after Titration.**—The recovery was performed as for methane XVII; 166 mg. or 79% was recovered from 211 mg. One recrystallization brought the m. p. to 96°; mixed m. p. with XVIII, no depression.

B. Methylation.—The sodium salt obtained by titrating 202 mg. of methane XVIII in benzene was treated with 3.0 cc. of dimethyl sulfate solution and the mixture refluxed for two hours. The product was treated as described under the dimethylation of XVII; yield, 180 mg. or 86%. After two recrystallizations from hexane, m. p. 125–127°; no depression with methane XXIII, m. p. 129°.

Reactions of 3,5,1',4'-Tetramethyl-4,3',5'-tricarbethoxydipyrromethane (XXII). **A. In Benzene; Attempted Titration.**—One hundred and ninety-nine milligrams (0.000475 mole) of methane XXII was dissolved in 5 cc. of benzene and treated with 0.00047 mole of sodium triphenylmethyl. As the addition was made, the colorless sodium salt settled out as a soapy mass and as time passed the solution took on a blue fluorescence and violet color indicating that condensation had taken place to some extent.³ On adding water to the solution, the violet color disappeared. The mixture was warmed to remove the benzene and ether, cooled and filtered. The solid was extracted with a small amount of hexane leaving 170 mg. of a yellow powder melting at 95–105°; after two crystallizations from alcohol and water, m. p. 110°; no depression with starting material.

B. Methylation.—Two hundred and twenty-eight milligrams (0.000545 mole) of methane XXII in 5.0 cc. of benzene was treated with 0.0005 mole of sodium triphenylmethyl and 1.0 cc. of dimethyl sulfate solution was added

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.

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[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*, **58**, 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).