[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY AND FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

# The Synthesis of Unsymmetrical N-Methyl Dipyrrylmethanes[1]

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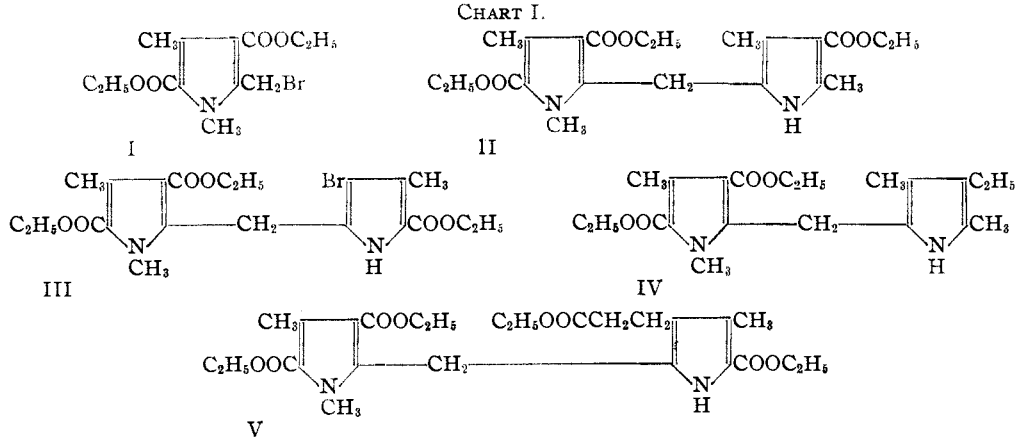
In 1927 Fischer and Stangler[3] mentioned the possibility that porphyrins might exist in isomeric forms in which the positions of hydrogens on the nuclear nitrogens were different. Corwin and Quattlebaum[4] proposed an experimental method for testing this possibility and pointed out the theoretical limitations to this type of isomerism. Rothemund[5] subsequently claimed to have prepared porphyrins exhibiting this type of isomerism although no experimental evidence was advanced to support this contention. It should be pointed out that the compounds prepared by Rothemund retain their differences through regeneration from salts with hydrochloric acid and regeneration from metallic complexes, two manipulations which exceed the limits for the stability of these isomers predicted by modern valence theory. No explanation for this apparent anomaly was advanced.

The method proposed by Corwin and Quattlebaum for the examination of "N-isomerism" in porphyrins was to prepare methylated porphyrins by direct methylation and by ring synthesis and to compare their properties. Previous papers in this series[6] have dealt with the study of N-methylated pyrroles and have uncovered numerous anomalous reactions, particularly in attempts to prepare dipyrrylmethenes. These anomalies have been shown to occur as a result of extensive cleavages of C–C bonds and appear most frequently in N-methylated derivatives where recombination of fragments is slowed up by the effect of the N-methyl group and other substituents. The results of these investigations have led us to inquire as to whether similar anomalies occur in reactions leading to dipyrrylmethanes, since these substances might serve equally as well as dipyrrylmethenes in condensations designed to lead to porphyrins.

Our first paper reported the synthesis of two symmetrical N-methyl dipyrrylmethanes. We now report an extension of this work to the synthesis of unsymmetrical N-methyl dipyrrylmethanes, exploiting a second general method for the synthesis of this type of compound (Chart I).

CHART I.




Compound I was condensed with the requisite pyrroles with free $\alpha$-positions to yield methanes II, III, IV and V. In the case of methane IV, it was found that kryptopyrrole did not condense under the usual reaction conditions but that the reaction could be forced by the use of kryptopyrrylmagnesium bromide.

It is apparent that the normal condensation can be prevented by the introduction of certain substituents in the ring containing the free $\alpha$-position. The converse of this proposition may also be demonstrated. By changing the $\beta$-

(1) Studies in the Pyrrole Series. VII. This paper is from the doctoral dissertation of Wm. M. Quattlebaum, Jr., Harvard University, 1934. The authors wish to express their appreciation of the guidance of Dr. James B. Conant in the initiation and direction of this work.

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(3) Fischer and Stangler, *Ann.*, **459**, 54 (1927).

(4) Corwin and Quattlebaum, THIS JOURNAL, **58**, 1081 (1936).

(5) Rothemund, *ibid.*, **61**, 2912 (1939).

(6) Corwin and co-workers, *ibid.*, **58**, 1086 (1936); **59**, 1973 (1937); **62**, 418 (1940); **63**, 1829 (1941).

carbethoxy group in compound I to propionic acid, the course of the reaction was changed and no crystalline compound could be obtained by condensation with four different $\alpha$-free pyrroles. Thus it can be concluded that the course of this reaction is markedly dependent upon the nature of the substituents upon each of the pyrrole rings entering into the reaction but that, unlike the case of the methenes, N–$CH_3$ as a substituent does not necessarily block the reaction.

The authors wish to acknowledge the aid of Mr. J. Gordon Erdman in refining some of the preparations described in this paper and performing some of the analyses and that of Mrs. G. Ware Wellwood in performing some of the remaining analyses.

## Experimental Part

**1,4-Dimethyl-2-bromomethyl-3,5-dicarbethoxypyrrole.** (I).—Twenty grams of 1,2,4-trimethyl-3,5-dicarbethoxypyrrole is placed in a 200-cc. three-neck round-bottom flask equipped with a mechanical stirrer, thermometer and dropping funnel. Glacial acetic acid (50 cc.) is then added. Bromine (50 g.) dissolved in 10 cc. of glacial acetic acid is run in slowly from the dropping funnel, the temperature being kept at 30–40°. The mixture is allowed to stand for one hour, and is then poured into a very large porcelain evaporating dish, placed in the hood and allowed to dry. The solid remaining is removed, dissolved in hot ligroin and decanted through a filter from a small amount of brown oily material. On cooling, the bromo-derivative crystallizes out in rosets; yield, 80%. The product may be recrystallized from glacial acetic acid after having been purified by the ligroin treatment; m. p. 82°.

*Anal.* Calcd. for $C_{13}H_{18}O_4NBr$: C, 46.99; H, 5.42. Found: C, 47.12; H, 5.57.

**1,4,3′,5′-Tetramethyl-3,5,4′-tricarbethoxydipyrrylmethane** (II).—Six and sixty-four hundredths grams of 1,4-dimethyl-2-bromomethyl-3,5-dicarbethoxypyrrole is dissolved in the least possible amount of absolute methyl alcohol and placed in a flask equipped with a reflux condenser; 3.34 g. of 2,4-dimethyl-3-carbethoxypyrrole is dissolved in a small quantity of absolute methanol and added to the solution of the bromo compound. The flask is then placed on the steam-bath and the contents heated nearly to the boiling point of the alcohol. A drop of hydrochloric acid is added and the mixture is heated under the reflux condenser for half an hour or until the methane crystallizes out. If crystallization does not take place within this time, a small amount of the alcohol is evaporated off. The methane is filtered off and recrystallized from methanol; yield, 75%; m. p. 110°.

*Anal.* Calcd. for $C_{22}H_{30}O_6N_2$: C, 63.00; H, 7.20. Found: C, 63.03; H, 7.30.

**2-Carboxyl-3-bromo-4-methyl-5-carbethoxypyrrole.**—In a 500-cc. three-neck flask equipped with motor stirrer, thermometer and dropping funnel are placed 51.5 g. of 2,4-dimethyl-3-bromo-5-carbethoxypyrrole and 250 cc. of glacial acetic acid. The flask is cooled in an ice-bath and at 14°, bromine (33 g.) added rapidly. The addition of 84.8 g. (52.5 cc.) of sulfuryl chloride is started at 14° and the temperature allowed to fall as far as possible without congealing the acetic acid. During the first half of the addition of the sulfuryl chloride, the temperature will not go below 11° but later it should be lowered to 0° by substituting a freezing mixture for the ice-bath. The addition requires one and one-half to two hours. The mixture is held at 0.2° for six hours. Water at room temperature is added drop by drop until the violence of the action diminishes and then more rapidly until the flask is full. The temperature is raised to 60° and held there for fifteen to thirty minutes. The solution is poured slowly into two liters of cold water and stirred to complete the coagulation of the precipitate. The precipitate is filtered off under a hood and washed with cold water. It is dissolved in alcohol and warmed to 60°. Dry powdered sodium bicarbonate is added to the alcoholic solution until no further evolution of carbon dioxide is noted. The solution is then poured very slowly and with constant stirring into five times its volume of cold water. The mixture is allowed to stand with occasional stirring for at least an hour to ensure complete precipitation of the aldehyde which is formed as a by-product. The aldehyde is removed by filtration and may be purified by recrystallization from the minimum amount of toluene. The acid is precipitated with hydrochloric acid, filtered, washed and dried at 50°; yield, 23 g. or 40%; m. p. 254° with decomposition.

*Anal.* Calcd. for $C_9H_{10}O_4NBr$: C, 39.13; H, 3.65. Found: C, 39.20; H, 3.82.

**3-Bromo-4-methyl-5-carbethoxypyrrole.**—The decarboxylation of the preceding compound is carried out as rapidly as possible (5–10 seconds) in three times its weight of glycerol. This preparation must be carried out under a good hood since acrolein is formed. Because of the necessity of working rapidly, the quantity used in this procedure is limited to 2.5 g.; yield, 40%; m. p. 179–183° with decomposition.

*Anal.* Calcd. for $C_8H_{10}O_2NBr$: C, 41.38; H, 4.31. Found: C, 41.34; H, 4.38.

**1,4,4′-Trimethyl-3,5,5′-tricarbethoxy-3′-bromodipyrrylmethane** (III).—Three and thirty-two hundredths grams of 1,4-dimethyl-2-bromomethyl-3,5-dicarbethoxypyrrole is condensed with 2.32 g. of 3-bromo-4-methyl-5-carbethoxypyrrole according to the procedure outlined for methane II above; yield, 3 g. or 62%; m. p. 142°.

*Anal.* Calcd. for $C_{21}H_{27}O_6N_2Br$: C, 52.17; H, 5.59. Found: C, 52.28; H, 5.64.

**1,4,3′,5′-Tetramethyl-4′-ethyl-3,5-dicarbethoxydipyrrylmethane** (IV).—In a 200-cc. three-neck flask equipped with stirrer and mercury seal, a reflux condenser and a dropping funnel, is placed 2.4 g. of magnesium turnings and a solution of 10.9 g. of ethyl bromide in 50 cc. of anhydrous ether is added over a period of one hour. 2,4-Dimethyl-3-ethylpyrrole (12.3 g.) in 40 cc. of anhydrous ether is added drop by drop to the solution of the Grignard reagent and then 23.2 g. of the 1,4-dimethyl-2-bromomethyl-3,5-dicarbethoxypyrrole, suspended in 200 cc. of anhydrous ether, is added slowly with stirring. After heating for several hours the product is decomposed by

pouring into ice water containing ammonium chloride. The ether layer is separated and the aqueous layer extracted with a fresh portion of ether. The combined ether layers are dried over anhydrous sodium sulfate and if necessary decolorized with a small quantity of activated charcoal. The clear filtrate, on evaporating to dryness, yields 21 g. or 56% of the methane which can be recrystallized from alcohol; m. p. 126°.

*Anal.* Calcd. for $C_{21}H_{30}O_4N_2$: C, 67.38; H, 8.02. Found: C, 67.36; H, 7.93.

**1,4,4'-Trimethyl-3,5,5'-tricarbethoxydipyrrylmethane-3'-propionic Acid Ethyl Ester** (V).—Three and thirty-two hundredths grams of 1,4-dimethyl-2-bromomethyl-3,5-dicarbethoxypyrrole is condensed with 2-carbethoxy-3-methyl-4-pyrrylpropionic acid according to the procedure outlined above for compound II, except that ethanol is substituted for methanol. It is necessary to evaporate off a portion of the solvent to bring about crystallization. A small seed is saved and the remainder recrystallized from purified hexane. The velocity of crystallization is small but large white crystals are obtained; m. p. 114°. The condensation is accompanied by esterification of the propionic acid group due to the conditions of the reaction; yield, 70% of the theoretical.

*Anal.* Calcd. for $C_{26}H_{36}O_6N_2$: C, 61.87; H, 7.20. Found: C, 61.84; H, 7.25.

**1,2,4-Trimethyl-3-formyl-5-carbethoxypyrrole.**—Twenty grams of 1,2,4-trimethyl-5-carbethoxypyrrole is dissolved in 800 cc. of anhydrous ether, 30 cc. of anhydrous hydrogen cyanide added and dry hydrogen chloride passed through for four hours. The ether is evaporated off, one liter of cold water added, the solution filtered and the clear filtrate warmed to 40°. On cooling, colorless needles separate out; m. p. 63–64°. The product can be recrystallized from a solution containing a small quantity of chloroform in petroleum ether.

*Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23. Found: C, 63.08; H, 7.28.

This substance was also prepared by methylation of 2,4-dimethyl-3-formyl-5-carbethoxypyrrole by the method outlined by Corwin and Quattlebaum for 2,4-dimethyl-3,5-dicarbethoxypyrrole; m. p. of crude product 58°; in mixed m. p. with product from procedure above, 57–58°.

**1,2,4-Trimethyl-5-carbethoxy-3-pyrrylacrylic Acid.**—Twenty-two grams of 1,2,4-trimethyl-3-formyl-5-carbethoxypyrrole and 12.2 g. of malonic acid is dissolved in 110 cc. of alcohol, the solution placed on the steam-bath, brought to a boil and freshly distilled aniline (11 cc.) added. Heating under reflux is continued for six to seven hours. The product usually began to separate after the first few hours. The flask is then removed from the steam-bath and the contents allowed to cool. The crystals are filtered off and washed with a small quantity of alcohol. The compound is recrystallized by dissolving in the least possible quantity of hot ethyl alcohol and adding hot water to turbidity. On cooling, the acrylic acid which separates is filtered off and dried; yield, 18 g. or 68%; m. p. 184–189°.

*Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 62.15; H, 6.77. Found: C, 62.13, 62.16; H, 6.91, 6.87.

**1,2,4-Trimethyl-5-carbethoxy-3-pyrrylpropionic Acid.**—Ten grams of 1,2,4-trimethyl-5-carbethoxy-3-pyrrylacrylic acid is placed in a 500-cc. Erlenmeyer flask, together with 150 cc. of water; the flask is placed on a shaking machine and 150 g. of 3% sodium amalgam added over a period of three hours at half-hour intervals. Shaking is continued for two hours after completing the addition of amalgam. The flask is then removed from the machine, the alkaline solution decanted, extracted once with ether, cooled with ice and neutralized with 30 cc. of 50% acetic acid. The propionic acid which separates is filtered, washed with water and dried. It is recrystallized from hot ethyl alcohol by adding water to incipient precipitation and allowing to cool; m. p. 153–154°; yield, 6.6 g. of recrystallized product.

*Anal.* Calcd. for $C_{13}H_{19}O_4N$: C, 61.66, H, 7.51. Found: C, 61.76; H, 7.42.

**1,4-Dimethyl-2-bromomethyl-5-carbethoxy-3-pyrrylpropionic Acid.**—Two and fifty-three hundredths grams of 1,2,4-trimethyl-5-carbethoxy-3-pyrrylpropionic acid is dissolved in 4 cc. of glacial acetic acid and the solution placed in a small three-neck flask. A solution of 2 g. of bromine in 8 cc. of acetic acid is added drop by drop with stirring. After standing for four hours the product usually separates out. If this is not the case, crystallization is initiated by rubbing the sides of the flask with a glass rod, then allowed to stand one hour longer, filtered and washed with the least possible amount of glacial acetic acid. A white product results which melts at 158° with decomposition.

*Anal.* Calcd. for $C_{13}H_{18}O_4NBr$: C, 47.00; H, 5.42. Found: C, 47.26; H, 5.59.

Attempts were made to bring about the condensation of this bromo compound with the following pyrroles: 2,4-dimethyl-3-ethylpyrrole, 2-carbethoxy-3-methyl-4-pyrrylpropionic acid, 2,4-dimethyl-3-pyrrylpropionic acid and 2-carbethoxy-3-methyl-4-ethylpyrrole by numerous variations of the technique which was used for methane II but no crystalline compounds could be obtained. In most cases oils resulted instead.

**1,2,4-Trimethyl-3-acetyl-5-carbethoxypyrrole.**[4]—Eleven and one-half grams of sodium wire and 500 cc. of dry *t*-amyl alcohol are placed in a flask provided with an air condenser fitted with a calcium chloride tube; 52 g. of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole dissolved in the least possible amount of dry tertiary amyl alcohol is added to the tertiary amylate solution with stirring and the solution warmed on the steam-bath for half an hour. Redistilled dimethyl sulfate (64 g.) is added with stirring and the mixture allowed to remain on the steam-bath for one hour, whereupon it is poured into two liters of water. The *t*-amyl alcohol layer is removed, washed with 1-1 ammonium hydroxide solution to remove any dimethyl sulfate which may be present and poured into one liter of water contained in a two-liter flask. The flask is tightly stoppered and vigorously shaken for several minutes, whereupon the pyrrole crystallizes out. After filtering and drying, the product is recrystallized from ethanol; yield, 42 g. or 80%; m. p. 60°.

Attempts were made to brominate 1,2,4-trimethyl-3-ethyl-5-carbethoxypyrrole, obtained by the catalytic hydrogenation of the acetylpyrrole, in glacial acetic acid and in carbon tetrachloride, but the only products were

highly colored oils from which it was not found possible to isolate a crystalline compound.

**1,4-Dimethyl-2-carboxyl-3-ethyl-5-carbethoxypyrrole.**—The procedure is essentially that of Fischer, Sturm and Friedrich.[7] The yield is improved if the ethereal solution of the pyrrole is thoroughly dried over anhydrous sodium sulfate before proceeding with the chlorination. To obtain a satisfactory product for analysis it is also necessary to substitute 10% sodium carbonate for the sodium hydroxide used earlier; the yield was 30% on one-gram lots. For purification, the acid is dissolved in the minimum volume of acetone at room temperature. To about five times this volume of water a small seed of the acid is added and the water is then added slowly and with vigorous stirring to the acetone. The acid crystallizes out rapidly. It can then be recrystallized from diethyl ether. The solubility in diethyl ether decreases markedly on repeated recrystallization; m. p. 149–150° with slight decomposition.

*Anal.* Calcd. for $C_{12}H_{17}O_4N$: C, 60.19; H, 7.11. Found: C, 60.23; H, 7.13.

**N-Methyl-methylethylmaleic Imide.**—Further studies indicate that this compound may be prepared readily by two further techniques. (a) Forty-six hundredths of a gram of sodium is dissolved in 100 cc. of dry *t*-amyl alcohol contained in a 500-cc. flask equipped with a reflux condenser; 1.4 g. of methylethylmaleic imide is added and the solution allowed to stand for ten minutes. Then 2.52 g. of redistilled dimethyl sulfate is added, the mixture allowed to stand for half an hour and then heated on the steam-bath for ten minutes. The solution is filtered and the *t*-amyl alcohol evaporated off under reduced pressure. The oil which remains is dissolved in ether and the ethereal solution washed several times with 1–1 ammonia solution and finally with water. On evaporating off the ether, an oil boiling at 215–221° bath temperature, Siwoloboff method, is obtained.

(7) Fischer, Sturm and Friedrich, *Ann.*, **461**, 269 (1928).

(b) Methylethylmaleic imide (1.39 g.) is dissolved in the least possible amount of absolute alcohol and a saturated solution of 0.56 g. of potassium hydroxide in absolute alcohol is added with stirring. The potassium salt crystallizes out and is filtered and washed with a small amount of absolute ethyl alcohol. This product is soluble in water and leaves a residue when heated on a silver spatula. The potassium salt is then heated for ten minutes at 160–170° with an excess of dimethyl sulfate. After cooling, the solution is extracted with ether and the excess dimethyl sulfate washed out with 1–1 ammonia solution. The ethereal solution is washed with water and then dried over anhydrous sodium sulfate. After evaporating off the ether, a colorless oil boiling at 214–221° (Siwoloboff method) is obtained; yield, 0.7 g. or 46%.

On fractionally distilling this material, using an 8 in. × 8 mm. tube for a column, two fractions were obtained. The first fraction failed to solidify when placed in an ice–salt mixture; some solid material separated from the second fraction under the same conditions. The second fraction lost this property on standing in the vacuum desiccator for several days, an indication that it was due to the presence of water. That the impurity was not methylethylmaleic imide was shown by the fact that both fractions on saponification gave methylamine free from ammonia.

## Summary

1. A group of unsymmetrical mono-N-methyldipyrrylmethanes has been prepared.

2. It has been demonstrated that the course of the unsymmetrical dipyrrylmethane condensation is strongly dependent upon the nature of the substituents upon each pyrrole ring entering the reaction.

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# An Anhydro Derivative of D-Mannosan<1,5>β<1,6> (presumably 3,4-Anhydro-D-talosan<1,5>β<1,6>)

BY RAYMOND M. HANN AND C. S. HUDSON

In a recent publication[1] from this Laboratory it was pointed out that 2,3-isopropylidene-D-mannosan<1,5>β<1,6> (I), a compound isolated as an intermediate in the preparation of D-mannosan<1,5>β<1,6> by the pyrolysis of vegetable ivory, should prove to be a useful substance for various syntheses. We have recently employed it in a synthesis of the disaccharide 4-[β-D-glucopyranosido]-D-mannose[2] and of crystalline 4-methyl-D-mannose[3]; the present communication describes its further use for the synthesis of a new type of sugar derivative, a 3,4-anhydro-D-talosan<1,5>β<1,6> (IV), which is an anhydro sugar anhydride, possessing three rings. The 2,3-isopropylidene-D-mannosan<1,5>β<1,6> (I) was converted to 2,3-isopropylidene-4-tosyl-D-mannosan<1,5>β<1,6> (II) by treatment with pyridine and *p*-toluenesulfonyl chloride. The isopropylidene group of the tosylated acetal (II) was removed by refluxing the compound in dilute acetic acid, and the solution on cooling deposited crystalline 4-tosyl-D-mannosan-

(1) Knauf, Hann and Hudson, THIS JOURNAL, **63**, 1447 (1941).
(2) Haskins, Hann and Hudson, *ibid.*, **63**, 1724 (1941).
(3) Haskins, Hann and Hudson, unpublished results.