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

β-Acetyldipyrrylmethanes; Their Self-condensation to Porphyrins[1,2,3]

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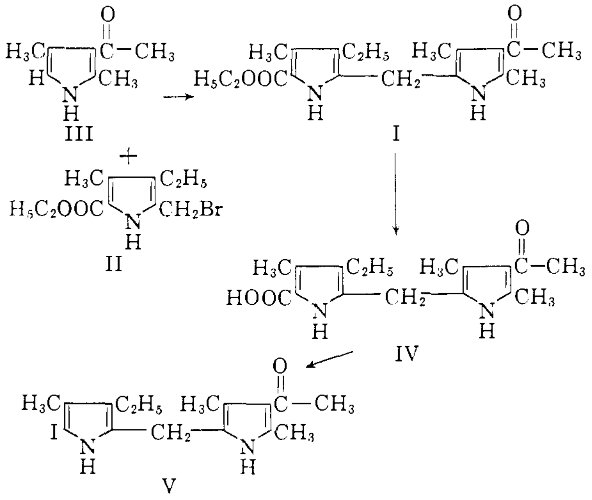
The synthesis of certain monoacetyldipyrrylmethanes is recorded. The self-condensation of α-free-α′-methylmonoacetyldipyrrylmethanes in the presence of cupric acetate in solvent naphthalene has been investigated in the search for a synthetic method for obtaining porphyrins from dipyrryl intermediates under conditions which permit retention of acetyl groups. Each of two isomeric monoacetyldipyrrylmethanes has been found to undergo self-condensation under these conditions to produce a mixture of isomeric diacetyldeuteroetioporphyrin copper complexes. Comparative X-ray powder patterns have established that the same diacetyldeuteroetioporphyrin copper complex is obtained from either of these monoacetyldipyrrylmethanes. The two alternative modes of synthesis show that it is in all probability the copper complex of 1,5-diacetyl-3,7-diethyl-2,4,6,8-tetramethylporphin. Isolation from the same self-condensation reaction mixture of chromatographically-separable products with identical absorption spectra (380–650 $m\mu$) indicates that these porphyrin syntheses are accompanied by a simultaneous rearrangement of monopyrryl structural units so as to give an altered sequence of substituent groups in at least certain of the porphyrin products. All porphyrins are obtained as their copper complexes, from which cupric ion is easily removed by brief treatment with concentrated sulfuric acid at room temperature.

A program of research directed toward the total synthesis of chlorophyll *a* has been in progress for some time in these laboratories. The projected synthetic route required the condensation of a β,β-dipyrrylpropionic ester with a monoacetyldipyrrylmethane under conditions which would permit the retention of labile substituent groups. The preparation of some β,β-dipyrrylpropionic esters has been reported in an earlier communication.[4] The present article is concerned with the synthesis of some monoacetyldipyrrylmethanes and with self-condensation of such methanes to give diacetylporphyrins. The investigation of porphyrin formation from these methanes was undertaken in an attempt to define condensation conditions which would permit the retention of the acetyl group.

Although in one reported instance[5] a monoacetylporphyrin has been synthesized directly from the reaction of two dipyrrylmethene hydrobromides with one another, it is well-known that acetyl[6a] or other acyl[6b] groups may be readily cleaved from the pyrrole ring by bromine or strong mineral acid. In a few instances porphyrins have been obtained from dipyrryl intermediates under relatively milder conditions, *e.g.*, *via* reaction at room temperature[7] or in mildly basic medium.[8] In the case of at least one such synthesis[8] the presence of a metallic salt proved essential to porphyrin formation.

It was decided to explore first the possibility that an α-iodo-α′-methylmonoacetyldipyrrylmethane might undergo self-condensation to a porphyrin in mildly basic medium. Because it was relatively accessible, the dipyrrylmethane I was selected as a starting point for this investigation. This methane was synthesized by the previously reported[9] condensation of bromomethylpyrrole II with α-free acetylpyrrole III. The methane ethyl ester I was converted to the corresponding acid IV by the action of sodium hydroxide, thence by iodinative decarboxylation[10,11] to iododipyrrylmethane V. Compounds IV and V have not been described previously in the literature; moreover, the latter substance appears to be the first reported α-iododipyrrylmethane. Exploratory condensation experiments demonstrated that iodomethane V does indeed yield a porphyrin product or products when heated briefly at 210–230° in quinoline solution. In each case, however, the wave lengths and relative intensities of the absorption peaks in the visible region indicated the predominant porphyrin to be an etioporphyrin or closely related compound rather than an acetylporphyrin. Thus it appeared that the acetyl group of the dipyrrylmethane had been either cleaved or reduced to an ethyl group during the condensation.



Since it was felt that iodine and/or iodide ion might well be responsible for the failure of the acetyl group to appear in the porphyrin product, a novel

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[1] Porphyrin Studies. XVII.

[2] Paper XVI, W. S. Caughey, A. H. Corwin and R. Singh, *J. Org. Chem.*, **25**, 290 (1960).

[3] This work was supported by a research grant (NSF-G 1195) from the National Science Foundation.

[4] G. G. Kleinspehn and A. H. Corwin, THIS JOURNAL, **76**, 5641 (1954).

[5] H. Fischer and A. Schormüller, *Ann.*, **473**, 211 (1929).

[6] H. Fischer and H. Orth, "Die Chemie des Pyrrols," Akademische Verlagsgesellschaft m.b.H., Leipzig, 1934, Vol. I, (a) p. 84 et seq., (b) p. 35, (c) p. 193, (d) p. 185.

[7] J. S. Andrews, A. H. Corwin and A. G. Sharp, THIS JOURNAL, **72**, 491 (1950).

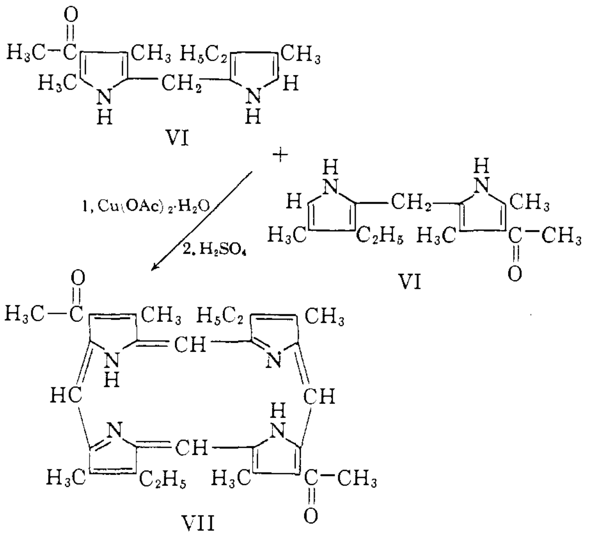
[8] A. H. Corwin and V. L. Sydow, *ibid.*, **75**, 4484 (1953).

[9] W. Schlesinger, A. H. Corwin and L. J. Sargent, *ibid.*, **72**, 2867 (1950).

[10] J. L. A. Webb and R. R. Threlkeld, *J. Org. Chem.*, **18**, 1409 (1953).

[11] G. G. Kleinspehn and A. H. Corwin, THIS JOURNAL, **75**, 5295 (1953).

approach to porphyrin synthesis was attempted using a halogen-free dipyrrylmethane intermediate, *i.e.*, an α-free-α′-methyldipyrrylmethane such as VI. Cupric acetate was employed to oxidize VI to the corresponding dipyrrylmethene or its copper complex, either of which might then undergo condensative aromatization to give the copper complex of the diacetyldeuteroetioporphyrin VII. The α-free dipyrrylmethane VI was obtained by thermal decarboxylation of the corresponding methane acid IV at temperatures comparable to those required for porphyrin formation. Thus it was not surprising to discover that the isolation of VI prior to condensation had little effect upon the yield of porphyrin products. It was therefore possible to use methane acid IV directly for porphyrin synthesis, decarboxylation and condensation being carried out in rapid succession. Approximately one hundred experiments were carried out using either IV or VI and varying the temperature, the solvent and the ratio of reactants in order to ascertain the optimum condensation conditions. Attempts were made to promote the condensation with a variety of other transition metal salts as well as cupric acetate, and the effect of certain dehydrogenation catalysts and aromatizing agents was investigated. The best yield of diacetyldeuteroetioporphyrin copper complex was obtained by decarboxylating IV in naphthalene to give VI, which without isolation was then heated with cupric acetate monohydrate to 210–230°. Chromatography of the crude product on Magnesol afforded several different porphyrin copper complexes. The nature of many of these is discussed in a subsequent portion of this paper. The predominant porphyrin fraction after purification by further chromatography and recrystallization was demonstrated by elemental analysis to be a diacetyldiethyltetramethylporphyrin (diacetyldeuteroetioporphyrin) copper complex. This material was converted to the corresponding porphyrin free base by treatment with concentrated sulfuric acid at room temperature. The visible absorption spectrum of the copper complex in dioxane solution showed absorption peaks at 596 and 545 mμ with a broad shoulder at about 530 mμ. Its infrared absorption spectrum in chloroform solution showed only a single absorption band at 1663 cm.$^{-1}$ because of its low solubility. This carbonyl stretching frequency absorption corresponds well with the band at 1658 cm.$^{-1}$ observed for diacetyldeuteroporphyrin IX dimethyl ester.[12] The free base obtained from the copper complex exhibited absorption maxima at 637, 583, 557.5 and 516 mμ in dioxane solution. The fact that this spectrum proved nearly identical with that of 2-desethyl-2,6-diacetylpyrroporphyrin XV methyl ester[13] or that of 2-desethyl-2-acetylrhodoporphyrin XV dimethyl ester[14] constitutes strong evidence that the two acetyl groups are present in opposite pyrrole rings of the porphyrin. Diacetylporphyrins such as diacetyldeuteroporphyrin IX dimethyl ester[15] or diacetyldeuteroetioporphyrin III,[16] which contain two acetyl groups located in adjacent pyrrole rings, are of a substantially different spectral type. The over-all yield of the synthetic diacetylporphyrin free base from methane acid IV was about 2%.



Confirmation of the structure of the diacetyldeuteroetioporphyrin product was next attempted by undertaking an alternative synthesis *via* the acetyldipyrrylmethane ester VIII, an isomer of I. It will be noted that either I or VIII after saponification, decarboxylation and subsequent self-condensation would be expected to yield the same diacetylporphyrin copper complex, the copper complex of porphyrin VII. Methane ester VIII had not been previously reported. Its synthesis was achieved starting from acetylpyrrolecarboxylic acid IX. The ring synthesis of IX from 3-amino-2-butanone and ethyl 2,4-dioxovalerate had been previously carried out, but the yield was not specified.[17] By controlling the *p*H of the reaction mixture during condensation,[18] it was possible to obtain IX in 18% yield. Acid IX was then esterified by alkylation of its conjugate base with diethyl sulfate, and the resulting ester X was reduced to XI by hydrogenation in the presence of palladium-on-carbon. Pyrroles X, XI and XIII had been reported earlier, but both X[19,20] and XI[21] had been prepared by different synthetic routes. Bromomethylpyrrole XIII[21] was obtained by employing the improved bromination procedure which proved successful in the preparation of its isomer (II). The known α-free acetylpyrrole XII,[17] obtained by decarboxylating acid IX, was condensed with XIII to form the new acetyldipyrrylmethane ester VIII, which was then saponified with base to give XIV. Like its isomer, methane acid IV, XIV was found to undergo decarboxylation and subsequent self-condensation in the presence of cupric acetate to provide a mixture of several

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(12) J. E. Falk and J. B. Willis, *Australian J. Sci. Research, Ser. A*, **4**, 579 (1951).

(13) A. Stern and H. Wenderlein, *Z. physik. Chem.*, **A175**, 405 (1936).

(14) A. Stern and H. Wenderlein, *ibid.*, **A174**, 81 (1935).

(15) F. Pruckner, *ibid.*, **A190**, 101 (1942).

(16) A. Stern and F. Pruckner, *ibid.*, **A180**, 321 (1937).

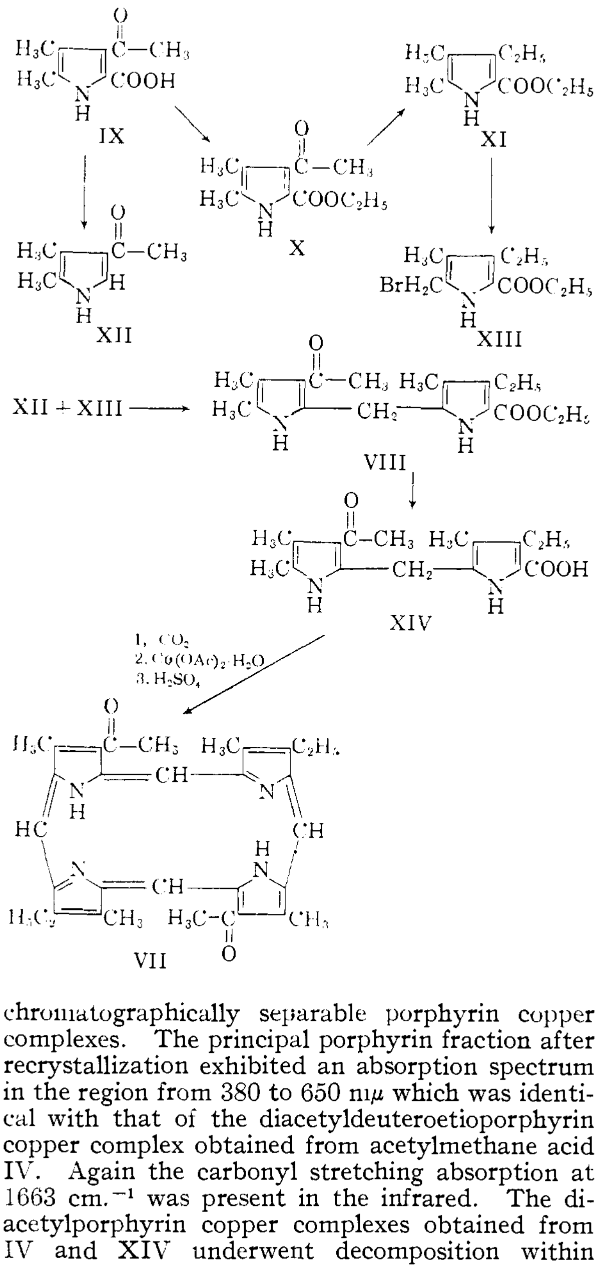
(17) O. Piloty and A. Blömer, *Ber.*, **45**, 3752 (1912).

(18) A. H. Corwin and R. H. Krieble, This Journal, **63**, 1829 (1941).

(19) H. Fischer and W. Kutscher, *Ann.*, **481**, 193 (1930).

(20) H. Fischer and E. Fink, *Z. physiol. Chem.*, **283**, 152 (1948).

(21) H. Fischer and G. Stangler, *Ann.*, **459**, 53 (1927).



chromatographically separable porphyrin copper complexes. The principal porphyrin fraction after recrystallization exhibited an absorption spectrum in the region from 380 to 650 mμ which was identical with that of the diacetyldeuteroetioporphyrin copper complex obtained from acetylmethane acid IV. Again the carbonyl stretching absorption at 1663 cm.$^{-1}$ was present in the infrared. The diacetylporphyrin copper complexes obtained from IV and XIV underwent decomposition within six degrees of one another between 340 and 350° without prior melting. Comparison of solubilities in dioxane, however, showed that the diacetyldeuteroetioporphyrin copper complex synthesized from methane acid IV was indeed less soluble in this solvent than was the spectrally identical substance obtained from methane acid XIV.

Because of the strong possibility that either or both of these products might consist of a mixture of isomeric porphyrin copper complexes, each product was separately rechromatographed on Magnesol with chloroform. Each product was resolved into two bands on the column, and in each case the lower band was eluted for further comparative study. The lower band fraction from IV and the lower band fraction from XIV were mixed together and co-chromatographed under the above conditions. A single band was obtained, thus showing identical chromatographic behavior. The two lower band fractions were also separately evaporated to dryness and each solid product was recrystallized for X-ray powder measurements. Comparison of the X-ray powder patterns for the lower band fraction from IV and for the corresponding fraction from XIV has shown that these two diacetyldeuteroetioporphyrin copper complexes are indeed identical. Other X-ray studies have shown[22,23] that porphyrin isomers afford distinctly different powder patterns. Since this diacetyldeuteroetioporphyrin copper complex was obtained both from dipyrrylmethane IV and from dipyrrylmethane XIV by alternative and independent syntheses, it is almost certainly the copper complex of porphyrin VII, *i.e.*, 1,5-diacetyl-3,7-diethyl-2,4,6,8-tetramethylporphyrin. Alternative synthesis is the method which has been consistently employed to establish the structure of synthetic porphyrins.

It has already been pointed out that a number of additional porphyrin copper complexes have been obtained as by-products from both IV and XIV. While these substances have not been submitted for elemental analysis, it has been possible to separate and characterize spectrophotometrically several of the chromatographic fractions obtained from IV as well as a few of the corresponding porphyrin free bases. The copper complexes are designated in the experimental section as 1, 2, 3A, 3B, 4A and 4B. Of these 3A and 3B exhibit identical absorption spectra in the visible region. Complexes 4A and 4B are also indistinguishable in this respect. The spectrum of 3A is very similar to that of the copper complex[24] of rhodoporphyrin XXI dimethyl ester, and the free base obtained from 3A closely resembles 6-acetylpyrroporphyrin XV methyl ester,[13] monoacetyldeuteroporphyrin IX dimethyl ester[15] and rhodoporphyrin XV dimethyl ester[25] with respect to its visible absorption spectrum. Thus it appears likely that 3A and 3B are copper complexes of isomeric monoacetyldeuteroetioporphyrins. It is probable that copper complex 1 is the complex of an etioporphyrin, but it is more difficult to suggest plausible structures for copper complexes 2, 4A and 4B on the basis of their absorption spectra.

The isolation of pairs of porphyrin copper complexes which exhibit identical visible absorption spectra strongly suggests that these porphyrin syntheses proceed in such a manner as to produce pairs of isomers. Elemental analysis both of the mixed diacetyldeuteroetioporphyrin copper complexes and of the derived mixed free bases obtained from IV has indicated that these mixtures are indeed mixtures of isomers. Thus the inference is that 3A is isomeric with 3B and that 4A and 4B are isomers. These experimental results are most simply explained by assuming that these porphyrin syntheses are accompanied by a simultaneous rearrangement of monopyrryl structural units so as to give an altered sequence of substituent groups in at

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(22) O. Kennard and C. Rimington, *Biochem. J.*, **55**, 105 (1953).

(23) G. G. Kleinspehn, A. E. Briod and W. S. Caughey, unpublished results presented at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959, Abstracts, p. 35-O.

(24) A. Stern, H. Wenderlein and H. Molvig, *Z. physik. Chem.*, **A177**, 40 (1936).

(25) A. Stern and H. Wenderlein, *ibid.*, **A170**, 337 (1934).

least certain of the porphyrin products. Rearrangement of this sort requires the scission of a carbon–carbon bond linking a pyrrole ring to a methane bridge. Since both dipyrrylmethanes[26,27] and tripyrrylmethanes[28,29] have been demonstrated to undergo such cleavages, rearrangement could occur *via* either of these types of intermediate. Related scissions have been proposed[30,31] to explain the preponderant formation of isomer type III porphyrins from monopyrryl intermediates. It is of interest to note that no diacetylporphyrin bearing acetyl groups in adjacent pyrrole rings has been found among the porphyrin products despite the evidence that there is some reshuffling of monopyrryl units. The absorption spectrum characteristic of diacetylporphyrins of this type is well-known[15,16] and easily recognized.

Acknowledgment.—The authors wish to thank Dr. Max Crute for carrying out the X-ray powder measurements reported herein.

Experimental[32]

Ethyl 5-(Bromomethyl)-4-ethyl-3-methyl-2-pyrrolecarboxylate (II).—The procedure described here is more rapid and convenient than that of Fischer and Ernst[33] as modified by Buc.[34] Buc first isolated a hydrobromide of II from bromination of ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate in glacial acetic acid, then converted it to free II by recrystallization from hot benzene. The present procedure obviates the necessity of isolating the intermediate hydrobromide.

Ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (31.8 g.), prepared by the palladium-catalyzed hydrogenation[34] of the corresponding 4-acetyl compound, was dissolved in 160 ml. of dry benzene at room temperature. A solution of 8.3 ml. of bromine in 80 ml. of benzene was then added dropwise with stirring during 40 min. and stirring was continued for an additional 5 min. The reaction mixture was heated briefly to boiling temperature to expel hydrogen bromide, diluted with 240 ml. of dry isoöctane, allowed to cool, then refrigerated. The product was filtered off, washed with 35 ml. of benzene–isoöctane (1:1) and dried *in vacuo* over sodium hydroxide and paraffin; yield 34.6 g. or 77%.

2,4-Dimethyl-3-pyrrolyl Methyl Ketone (III).—4-Acetyl-3,5-dimethyl-2-pyrrolecarboxylic acid[6c] was thermally decarboxylated by the procedure described[4] for the preparation of ethyl 4,5-dimethyl-3-pyrrolecarboxylate. After codistillation of the product with glycerol, it was precipitated first from the glycerol–ethanol distillate, then from ethanol solution by pouring each time into an excess of water; yield of III, 82%, m.p. 137–139°, lit.[6d] 137°.

Ethyl 5-[(4-Acetyl-3,5-dimethyl-2-pyrrolyl)-methyl]-4-ethyl-3-methyl-2-pyrrolecarboxylate (I).—This dipyrrylmethane was prepared by carrying out the condensation of pyrrole II with pyrrole III in essentially the manner described by Schlesinger, Corwin and Sargent.[9] While the yields of crude product were good, the crude was rather impure and frequently began to melt in the range 135–145°. It was generally necessary to recrystallize three times from 50–60% aqueous ethanol or from absolute methanol. A product of minimum m.p. 172.5–175° was obtained in yields varying from 32 to 59%, lit.[9] 174–175°.

5-[(4-Acetyl-3,5-dimethyl-2-pyrrolyl)-methyl]-4-ethyl-3-methyl-2-pyrrolecarboxylic Acid (IV).—The saponification of dipyrrylmethane ester I was accomplished by refluxing 14.0 g. of I in 105 ml. of ethanol with a solution of 3.5 g. of sodium hydroxide in 12.5 ml. of water for 3 hr., then pouring the reaction mixture into 250 ml. of water, and allowing it to stand for several hours at room temperature. After filtration of the solution and addition of 200 g. of ice to the filtrate the acid was precipitated by acidification with 20 ml. of 1:1 acetic acid–water. The product was collected on the filter, washed with water and dried *in vacuo* to a constant weight of 12.5 g. (97% yield). A small portion of the crude was recrystallized from ethanol–water for analysis to give a sample melting with decomposition at 220–225° when heated rapidly. Prior to analysis the material was dried *in vacuo* at 85–100° for 50 min.

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33. Found: C, 67.18; H, 7.73.

There is evidence that this acid crystallizes from ethanol as the fairly stable monosolvated compound. A sample of the crude acid recrystallized first from acetone–water, then from ethanol and dried *in vacuo* for 2 hr. at room temperature was analyzed.

Anal. Calcd. for $C_{17}H_{22}N_2O_3 \cdot C_2H_5OH$: C, 65.49; H, 8.10; OC_2H_5, 12.9. Found: C, 65.60; H, 7.96; OC_2H_5, 11.0.

5-[(3-Ethyl-5-iodo-4-methyl-2-pyrrolyl)-methyl]-2,4-dimethyl-3-pyrrolyl Methyl Ketone (V).—Dipyrrylmethane acid IV was converted to its sodium salt by heating 410 mg. of IV and 330 mg. of sodium bicarbonate with 5 ml. of water and 16 ml. of methanol until only a small amount of sodium bicarbonate remained undissolved. The mixture was then cooled to room temperature. A solution of 340 mg. of iodine in 5 ml. of methanol was added dropwise with stirring while the reaction mixture was immersed in an ice–water-bath. When the addition was complete the mixture was refrigerated for 3 hr. The crude product was collected on a filter; yield 0.41 g. or 79%. A sample was recrystallized for analysis by taking this product up in ethanol at room temperature, adding water to turbidity, then refrigerating, filtering, washing and drying *in vacuo* at room temperature.

Anal. Calcd. for $C_{16}H_{21}N_2OI$: C, 50.01; H, 5.51. Found: C, 50.30, 50.10; H, 5.67, 5.74.

5-[(3-Ethyl-4-methyl-2-pyrrolyl)-methyl]-2,4-dimethyl-3-pyrrolyl Methyl Ketone (VI).—This α-free acetyldipyrrylmethane was obtained by decarboxylation of dipyrrylmethane acid IV. In a filter tube (test-tube with side tube) was placed 1.55 g. of IV. A slow stream of nitrogen was passed through the tube while the contents were heated at 190–220° (bath temperature) in an oil-bath for 11 min. During this time considerable gas evolution took place. The reaction mixture was cooled somewhat and triturated with 8 ml. of isoöctane until crystallization was complete. The product was collected on a filter and washed with more isoöctane. Sublimation of the crude product *in vacuo* afforded purer material of m.p. 132–134°. The analytical sample was obtained by recrystallization of the crude substance from ethanol–water.

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58. Found: C, 73.57; H, 8.66.

3-Acetyl-4,5-dimethyl-2-pyrrolecarboxylic Acid (IX).—The preparative procedure employed is very similar to that devised by Corwin and Krieble[18] for the preparation of the 3-ethyl ester of 4,5-dimethyl-2,3-pyrroledicarboxylic acid. Pyrrole acid IX was first obtained in unspecified yield by Piloty and Blömer[17] from the condensation of 3-amino-2-butanone with ethyl 2,4-dioxovalerate. In the present work 3-amino-2-butanone[18] has been condensed with the sodio derivatives both of ethyl[35] and of methyl[36] 2,4-dioxovalerate at 80–85°, the *p*H being held in the range 5 to 7 (Hydrion paper). When the reaction had been completed, the reaction mixture was cooled to room temperature and, after adjustment of the *p*H to 3 with concd. hydrochloric acid, it was refrigerated. The crude, somewhat tarry product obtained on filtration was taken up in hot excess 10% aqueous potassium bicarbonate solution and treated with Norit A. After removal of the Norit, the solution was extracted once with ether to remove oily bicarbonate-insoluble material. Acidification of the aqueous phase with hydrochloric acid to

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(26) A. Treibs and G. Fritz, *Ann.*, **611**, 162 (1958).

(27) A. Treibs and H. G. Kolm, *ibid.*, **614**, 199 (1958).

(28) A. H. Corwin and J. S. Andrews, THIS JOURNAL, **58**, 1087 (1936).

(29) A. H. Corwin and J. S. Andrews, *ibid.*, **59**, 1973 (1937).

(30) E. Bullock, A. W. Johnson, E. Markham and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958).

(31) A. Treibs and W. Ott, *Ann.*, **615**, 137 (1958).

(32) All melting points unless otherwise indicated were determined on the Fisher–Johns melting point apparatus.

(33) H. Fischer and P. Ernst, *Ann.*, **447**, 139 (1926).

(34) S. R. Buc, Dissertation, The Johns Hopkins University, 1938, pp. 56-60.

(35) C. S. Marvel and E. E. Dreger, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 238.

(36) M. Freri, *Gazz. chim. ital.*, **68**, 612 (1938).

$pH \leq 1$ caused separation of the desired pyrrole acid, which after filtration, resuspension in water and refiltration was dried *in vacuo;* m.p. 201–209° dec. with previous softening, lit. m.p. 204° dec. The highest yield was obtained when the sodio derivative of methyl 2,4-dioxovalerate was used; yield 18% based upon 3-amino-2-butanone chlorostannate.

Ethyl 3-Acetyl-4,5-dimethyl-2-pyrrolecarboxylate (X).—This pyrrole had been previously synthesized *via* the acetylation of ethyl 4,5-dimethyl-2-pyrrolecarboxylate.[19,20] It has now been obtained by esterification of the pyrrole acid IX (A) with ethanol and hydrogen chloride and (B) with diethyl sulfate in a bicarbonate solution of the pyrrole acid. Method (B) has proved the more satisfactory.

The pyrrole acid IX (20.8 g.) and potassium bicarbonate (35 g.) were added to 230 ml. of ethanol and the mixture was refluxed for several minutes to ensure conversion of the acid to its potassium salt. After the addition of 30 ml. of diethyl sulfate the mixture was refluxed for 90 min., then 1150 ml. of ice-water was introduced prior to refrigeration. The product was filtered off, washed liberally with water and dried; yield 17.7 g. or 74%, m.p. 136–137.5°. Recrystallization from ethanol gave 14.4 g. of the ester, m.p. 138.5–140°, lit.[19,20] 137°. Acidification of the first filtrate to pH 2 with hydrochloric acid precipitated 3.5 g. or 17% of unesterified acid IX.

Ethyl 3-Ethyl-4,5-dimethyl-2-pyrrolecarboxylate (XI).—The synthesis of this pyrrole from the Grignard magnesio derivative of 4-ethyl-2,3-dimethylpyrrole and ethyl chloroformate has been described.[21] The hydrogenation of acetylpyrrolecarboxylic ester X has not been previously reported. The procedure described here is essentially that described by Corwin and Buc for the preparation of the isomeric ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate.[34]

In a thick-walled bottle was placed 250 ml. of ethanol, 2.5 ml. of aqueous 10% palladous chloride solution, 15.5 g. of pyrrole X and 5.0 g. of Norit A. Hydrogenation was begun at a gauge pressure of 31.4 p.s.i. and shaking was continued for a total of 36 hr. After the first 6 hr. of the hydrogenation, the hydrogen pressure was once more raised to 31.4 p.s.i. gauge. The total hydrogen uptake observed corresponded to 90–100% of the theoretical. The catalyst was removed by filtration, extracted with 50 ml. of boiling ethanol, and the total filtrate was poured into five times its volume of water with stirring. After refrigerating for a few hours the precipitated pyrrole was filtered off and dried. The crude product melted over a 13° range. By repeated recrystallization of the crude product from boiling 70% ethanol, cooling only to room temperature and by repurifying material reclaimed from the mother liquor, 7.5 g. or 52% yield of product of m.p. 95.5–97.5° was obtained, lit.[21] 97°.

Ethyl 5-(Bromomethyl)-3-ethyl-4-methyl-2-pyrrolecarboxylate (XIII).—The bromination of ethyl 3-ethyl-4,5-dimethyl-2-pyrrolecarboxylate (XI) was carried out by the procedure described for the preparation of the isomeric bromomethylpyrrole (II). In one run the product obtained by cooling the reaction mixture to room temperature without addition of isoöctane showed m.p. 129–133° with dec., lit.[21] 134°. However, a larger yield (68%) could be obtained by diluting with isoöctane and refrigerating as described in the preparation of II.

4,5-Dimethyl-3-pyrrolyl Methyl Ketone (XII).—3-Acetyl-4,5-dimethyl-2-pyrrolecarboxylic acid (IX) was decarboxylated by essentially the procedure used to prepare pyrrole III. However, in this case a slow stream of nitrogen gas was passed through the apparatus during the decarboxylation. The product was obtained by adding ethanol to the glycerol-containing distillate, then pouring the solution into excess water. The yield ranged from 64 to 74%, m.p. 137–139°, lit.[17] 137°.

Ethyl 5-[(3-Acetyl-4,5-dimethyl-2-pyrrolyl)-methyl]-3-ethyl-4-methyl-2-pyrrolecarboxylate (VIII).—This previously unreported dipyrrylmethane was prepared by condensation of bromomethylpyrrole XIII and acetylpyrrole XII using essentially the procedure described by Schlesinger, Corwin and Sargent[9] for the preparation of isomeric dipyrrylmethane I. Yields of pure product were low, ranging from 16 to 26%. The best recrystallization results were obtained using either methanol or toluene. The analytically pure material melted at 170–171°.

Anal. Calcd. for $C_{19}H_{26}N_2O_3$: C, 69.07; H, 7.93. Found: C, 69.06; H, 8.01.

5-[(3-Acetyl-4,5-dimethyl-2-pyrrolyl)-methyl]-3-ethyl-4-methyl-2-pyrrolecarboxylic Acid (XIV).—This dipyrrylmethane acid was prepared from its ethyl ester VIII by the procedure described for preparation of isomeric dipyrrylmethane acid IV. The yield of crude acid was 90%. The analytical sample was prepared by recrystallization from ethanol–water, then dried *in vacuo* at 75–78° for 1 hr.; m.p. 141–146° dec. This acid exhibits a higher solubility in ethanol than does the isomeric acid IV.

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.27. Found: C, 68.06; H, 7.46; N, 9.38.

Preparation of Porphyrins from Dipyrrylmethane Acid IV. (a) Chromatographic Separation and Spectral Characterization of the Copper Porphyrin Complexes.—A mixture of 50 mg. of dipyrrylmethane acid IV and 1.5 g. of naphthalene was heated to 190° (oil-bath temp.) to effect decarboxylation and the mixture was then cooled to incipient solidification, at which point 45 mg. of cupric acetate monohydrate was introduced. The mixture was replaced in the oil-bath at 120° and the bath temperature was increased to 210° during 5.5 min., then held at 210–230° for an additional 5.5 min.

The partially cooled mixture was next taken up in ethylene dichloride to give a dark-colored suspension which was chromatographed on Woelm neutral alumina #2 (30 g.) using a column of 2.0-cm. diameter. Four fractions were collected: (A) the faintly colored forerun, (B) a pink zone, (C) a purple-blue zone and (D) a red zone.

These zones were not cleanly separated on the first chromatogram. Zone A contained a trace of porphyrin 1; zone B after evaporation to dryness was rechromatographed on Magnesol with ethylene dichloride, then chloroform to give a little additional porphyrin 1 as well as porphyrins 3A and 3B. Rechromatography of zone C with ethylene dichloride on Woelm neutral alumina #2 gave a little additional 3A and/or 3B, then porphyrin 2; porphyrin 5 was eluted with chloroform, then acetone. Porphyrin 2 was rechromatographed with ethylene dichloride on Magnesol. Porphyrin 5 was further purified by rechromatographing repeatedly on Magnesol with chloroform–ethyl acetate. Zone D was rechromatographed on Magnesol with ethylene dichloride, then chloroform to give products 4A and 4B.

In the foregoing description the porphyrin copper complexes have been designated by numbers which express the order of increasing affinity for the adsorbent Magnesol. Thus 1 is the most easily eluted fraction, while elution of 5 requires the most polar solvent. It will be noted from the data of Table I that the wave lengths of absorption maxima in the visible region increase in this same order. The order of increasing affinity for neutral Woelm alumina #2 is expressed by a different sequence: 1, 3A and 3B, 2, 5, 4A and 4B. It should be noted that Magnesol affords cleaner separations than does neutral Woelm alumina #2. Table I presents the results of spectrophotometric determination of absorption spectrum characteristics of these copper complexes.

TABLE I

RELATIVE EXTINCTION COEFFICIENTS[a] AND WAVE LENGTHS OF ABSORPTION MAXIMA FOR PORPHYRIN COPPER COMPLEXES IN DIOXANE SOLUTION

Porphyrin copper complex	Yield, %	Maxima λ in mμ		Relative ϵ values[a]	
		I	II	I	II
1	<0.15	561	525	I > II	
2	.15[c]	564	528.5	1.00	0.77
3A	.25[c]	580	536.5	1.00	.48
3B	.20[c]	580	536.5	1.00	.49
4A	.20[c]	584.5	540	1.00	.62
4B	.55[c]	584.5	540	1.00	.62
5	.90	597	545	1.00	.27
RCC[b]	..	578	534	1.00	.49

[a] These values have been obtained for each copper complex by arbitrarily assigning a value of 1.00 to peak I. [b] RCC = rhodoporphyrin XXI dimethyl ester copper complex; these data were obtained by Stern, Wenderlein and Molvig[24] and are included for comparison. [c] These spectrophotometrically determined yields are only approximate; in each case the value was calculated by using the reported molecular extinction coefficients of a known porphyrin copper complex with similar spectral characteristics.

(b) **Preparation and Spectral Characterization of Porphyrin Free Bases from Certain of the Corresponding Copper Complexes.**—Certain of the above copper complexes, namely 3A, 4A and 5, were converted to the corresponding free bases by dissolving in concd. sulfuric acid at room temperature, adding glacial acetic acid, then water, then pyridine. The liquid phase containing the porphyrin free base was evaporated to near dryness. The residual solid was then chromatographed on neutral Woelm alumina #1, and after evaporation of the eluate to dryness, the residue was dissolved in dioxane. The spectral characteristics of the resulting free bases are presented in Table II.

TABLE II

RELATIVE EXTINCTION COEFFICIENTS[a] AND WAVE LENGTHS OF ABSORPTION MAXIMA FOR PORPHYRIN FREE BASES IN DIOXANE SOLUTION

Porphyrin free base	Maxima λ in mμ				Relative ε values[a]			
	1	II	III	IV	1	II	III	IV
From 3A	632.5	573	545.5	506.5	0.16	0.83	1.33	1.00
From 4A	637	584	549.5	512.5	.24	0.88	1.16	1.00
From 5	637	583	557.5	516	.30	1.28	2.17	1.00
AP[b]	632	575	545	507	.17	0.71	1.19	1.00
DDP[c]	637	583	558	515	.24	1.36	2.38	1.00

[a] These values have been obtained for each free base by arbitrarily assigning a value of 1.00 to peak IV. [b] AP = 6-acetylpyrroporphyrin XV methyl ester. [c] DDP = 2-desethyl-2,6-diacetylpyrroporphyrin XV methyl ester. Data for AP and DDP are those of Stern and Wenderlein[13] and are included for comparison.

(c) **Preparation and Isolation of Diacetyldeuteroetioporphyrin Copper Complex from Methane Acid IV.**—The following procedure was used in order to obtain a substantial amount of product. Twenty runs of this size were made. One hundred milligrams of dipyrrylmethane acid IV and 360 mg. of cupric acetate monohydrate were triturated to give an intimate mixture, then 3.0 g. of naphthalene was mixed in thoroughly. The reaction mixture was introduced into an oil-bath previously heated to the range 100–140°. Temperature was increased during 3.5 to 5.5 minutes to 215° and was held in the range 215–235° for 5 minutes. The reaction mixture was allowed to cool to 100°, then taken up in ethylene dichloride for chromatographic purification as described for porphyrin 5 under (a). Products of twenty such runs were combined before purification. After filtration of the final purified chromatographic fraction to remove particles of Magnesol, the diacetyldeuteroetioporphyrin copper complex fraction was taken to dryness *in vacuo*. The residue was crystallized once from 450 ml. of 1:2 chloroform–methanol to give 44 mg. or 2.2% of product. An analytical sample was prepared by recrystallizing twice more from chloroform–methanol, then drying at 110–120° for 1 hr. *in vacuo*. The substance does not melt when heated on the Köfler hot-stage, but a color change from green to brown at 344–348° signalizes decomposition; absorption spectrum (380–650 mμ) in ethylene dichloride solution, λ_{max}: I, 595 mμ; IIa, 544 mμ; IIb, 525 mμ; Soret, 409 mμ; λ_{min}: I, 560.5 mμ; II, 532 mμ; III, 475 mμ. ϵ_{max}: I, 25,200; IIa, 6,300; IIb, 5,800; Soret, 192,000; ϵ_{min}: I, 4,500; II, 5,700; III, 2,000.

Anal. Calcd. for $C_{32}H_{32}N_4O_2Cu$: C, 67.65; H, 5.68. Found: C, 67.39; H, 5.67.

(d) **Conversion of Diacetyldeuteroetioporphyrin Copper Complex to Diacetyldeuteroetioporphyrin Free Base.**—Nineteen and four-tenths milligrams of the copper complex was dissolved in 5 ml. of concd. sulfuric acid to give a bright green solution. Addition of 40 g. of ice changed the color to blue-purple with gradual precipitation of the solid porphyrin. The product was filtered off and washed liberally with water; yield 17 mg. of crude product. This was recrystallized once from 150 ml. of 1:1 chloroform–methanol to give 13.5 mg. of porphyrin free base. One further recrystallization from the same solvent followed by drying at 110–120° for 2 hr. *in vacuo* afforded the analytically pure purple crystalline substance. Heating to 350° on the Köfler hot-stage brought about a gradual decomposition; absorption spectrum (380–650 mμ) in ethylene dichloride solution, λ_{max}: I, 635 mμ; II, 580 mμ; III, 557.5 mμ; IV, 515.5 mμ; Soret, 410 mμ; λ_{min}: I, 618 mμ; II, 575 mμ; III, 531.5 mμ; IV, 458.5 mμ; ϵ_{max}: I, 2,000; II, 11,800; III, 18,500; IV, 7,200; Soret, 225,000; ϵ_{min}: I, 950; II, 11,500; III, 4,200; IV, 1,000.

Anal. Calcd. for $C_{32}H_{34}N_4O_2$: C, 75.86; H, 6.76. Found: C, 75.48; H, 6.82.

Preparation and Isolation of Diacetyldeuteroetioporphyrin Copper Complex from Methane Acid XIV.—The procedure is essentially that described above in (c) using the isomeric acid IV. In this instance again twenty condensations were carried out, but in each condensation only 25 mg. of methane acid XIV, 90 mg. of cupric acetate monohydrate and 750 mg. of naphthalene were used. Most of the by-products observed during chromatographic purification appeared similar to those obtained from methane acid IV. Evaporation of final chromatographic fraction to dryness and recrystallization of the residue from 25 ml. of chloroform and 85 ml. of methanol gave 5.0 mg. of product or 1.1% yield. The substance received one more recrystallization from chloroform–methanol. It does not melt when heated on the Köfler hot-stage, but a color change from green to brown at 340–342° signifies decomposition. This diacetyldeuteroetioporphyrin copper complex exhibits a greater solubility in dioxane than does the analogous product obtained from methane acid IV; absorption spectrum (380–650 mμ) in ethylene dichloride solution, λ_{max}: I, 595 mμ; IIa, 544 mμ; IIb, 526 mμ; Soret, 409.5 mμ; λ_{min}: I, 560.5 mμ; II, 531 mμ; III, 475.5 mμ. ϵ_{max}: I, 25,500; IIa, 6,500; IIb, 6,100; Soret, 191,000; ϵ_{min}: I, 4,700; II, 6,000; III, 2,100.

Separation of the Isomeric Components of the Diacetyldeuteroetioporphyrin Copper Complex Product Obtained from Methane Acid IV.—The diacetyldeuteroetioporphyrin copper complex product was chromatographed in chloroform solution on Magnesol. Two bands of similar color developed and the lower of these was eluted. The residue obtained upon evaporation of the eluate to dryness was crystallized from chloroform–methanol.

Separation of the Isomeric Components of the Diacetyldeuteroetioporphyrin Copper Complex Product Obtained from Methane Acid XIV.—This diacetyldeuteroetioporphyrin copper complex product was separated into two components using the same procedure. Once again the lower band was eluted, and its residue was purified by recrystallization as in the case of the product obtained from IV.

Comparison of these Eluted Diacetyldeuteroetioporphyrin Copper Complex Components from IV and XIV. (a) Chromatographic Comparison.—A portion of the lower band eluate obtained from IV and a portion of that obtained from XIV were adsorbed on the same Magnesol column. Development with chloroform caused no band separation; a single band remained.

(b) **X-Ray Powder Pattern Comparison.**—X-Ray powder measurements showed that the crystalline product obtained from either lower band eluate was the same substance. Thus the same diacetyldeuteroetioporphyrin copper complex has been synthesized from XIV as well as from IV.

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