ties of these compounds is worthy of comment. The results were checked several times and are believed to be accurate within 30%. The diethylaminoethylphenyl urethan is less active than either of the propanol homologs, which, again, is in accord with previous observations on the influence of the length of the alcohol chain, but it is no less toxic. The propanol compounds are more effective on the exposed nerve, by the test which measures onset time rather than duration, than the corresponding mono- and diphenyl urethans of dialkylamino propanediols[1a] but the reverse is usually true with respect to corneal anesthesia. Other comparative tests indicate that the diphenyl urethans of propanediols (such as diothane) are more effective as topical anesthetics, and while giving a slower onset time likewise give considerably more prolonged duration of anesthesia following intradermal injection.

The phenyl urethans here reported are more active on the rabbit's cornea than such of the isomeric *p*-aminobenzoates as have been prepared and tested.[2,3] This same behavior has been observed for the corresponding esters of piperidinopropanediol[7] as well as for the phenyl urethan and *p*-aminobenzoate of 2-diethylamino-3-hydroxy-1,2,3,4-tetrahydronaphthalene.[8] These facts prompt the suggestion that the phenyl urethan configuration confers more topical anesthetic activity upon a molecule than does the isomeric *p*-aminobenzoate group.

Acknowledgment.—We wish to thank Dr. R. S. Shelton for assisting in the pharmacological work and Mr. Karl Bambach for the analyses.

Summary

The phenyl urethans of a number of dialkylaminopropanols have been prepared and shown to have local anesthetic properties. It is suggested that the phenyl urethan group is more active in causing anesthesia of the mucous surfaces than the isomeric *p*-aminobenzoate group.

(7) E. W. Scott and T. H. Rider, THIS JOURNAL, **55**, 804 (1933).
(8) E. S. Cook and A. J. Hill, to be published.

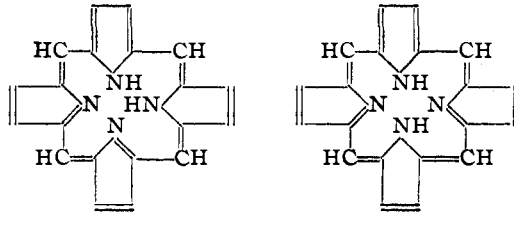
CINCINNATI, OHIO RECEIVED APRIL 6, 1936

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Studies in the Pyrrole Series. I. The Preparation of Certain N-Methyl Pyrroles[1]

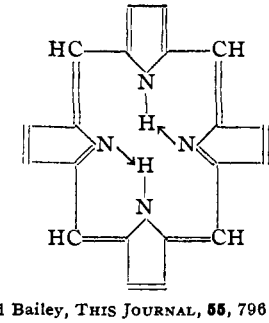
BY ALSOPH H. CORWIN[2] AND WM. M. QUATTLEBAUM, JR.[3]

If we accept Küster's formulation of the porphyrin nucleus as proved and exclude "resonance isomers," the following isomeric forms should be possible



These will be referred to as N-isomers.

Fischer[4] has suggested the simpler possibility of N-isomerism in di-pyrryl methenes but has not demonstrated its existence. Since N-isomers of the salts of methenes with mineral acids would be "resonance isomers," a separation should be achieved only by fractionation of the free bases. Likewise with the porphyrins, the salts with acids would be "resonance isomers." As a result we should not expect to find examples of N-isomerism among the synthetic porphyrins made by acid melts unless the free bases had been fractionated subsequently by a procedure not involving the use of acid. Conant and Bailey[5] have pointed out that differences between N-isomers should be destroyed by conversion into metallic complexes but found no porphyrins which exhibited this phenomenon.

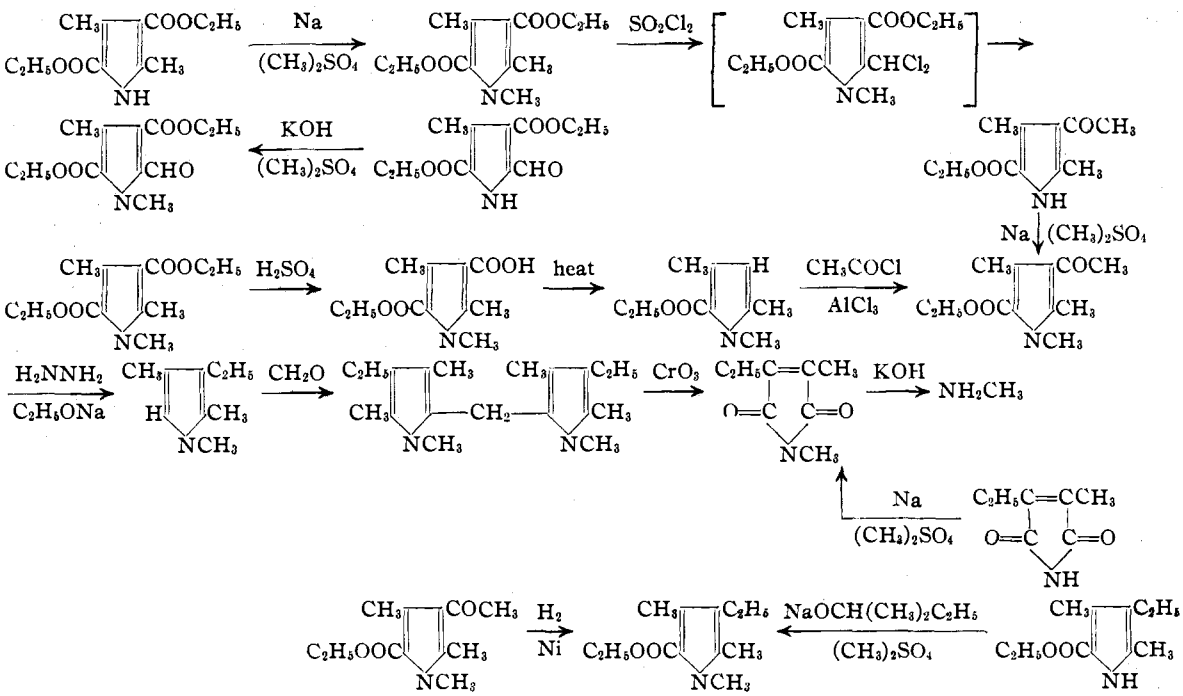


(1) From the doctoral dissertations of Alsoph H. Corwin, Harvard University, 1932, and Wm. M. Quattlebaum, Jr., Harvard University, 1934. The authors wish to acknowledge their indebtedness to Dr. James B. Conant for suggesting this field of research and their appreciation of his advice and guidance in the direction of the work.
(2) Present address, Department of Chemistry, The Johns Hopkins University, Baltimore, Md.
(3) Present address, Carbide and Carbon Chemicals Corp., South Charleston, W. Va.
(4) Fischer, *Z. physiol. Chem.*, **128**, 63 (1923).
(5) Conant and Bailey, THIS JOURNAL, **55**, 796 (1933).

An examination of a space model of a porphyrin suggests the possibility that the adjacent secondary and tertiary nitrogens might be joined by a hydrogen bridge.

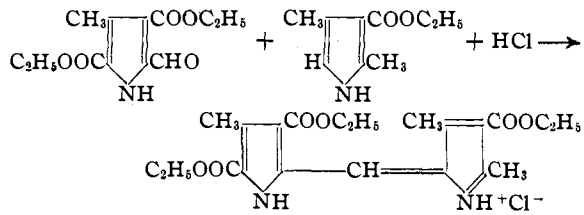
In such a case the predicated N-isomerism would not appear but might give way to another type in which the H bridges exchanged their partners.[6] Substitution of a functional group for hydrogen would destroy the latter isomerism and create the appearance that the original porphyrins were N-isomers.

To test the theoretical considerations presented, the question of N-isomerism is being submitted to experimental examination. It is proposed to synthesize porphyrins from compounds suited to the determination of the positions of the methylated nitrogens with reference to the unmethylated nitrogens. It is then proposed to N-methylate porphyrins and to compare the products with those prepared by synthesis. The first phase of this problem is the preparation and proofs of the structures of certain N-methyl pyrroles. Starting with Knorr's pyrrole (2,4-dimethyl-3,5-dicarbethoxypyrrole) the following interrelationships have been established



That the methyl group remains attached to nitrogen through all these reactions is shown by the fact that methylamine free from ammonia is obtained by the hydrolysis of N-methylmethylethylmaleic imide. The di-N-methyldipyrrylmethane indicated is the first completely alkylated dipyrrylmethane to be obtained by condensation with formaldehyde, despite many attempts.[7]

The second phase of the problem was the synthesis of N-methyl methenes. Since the simplest unsymmetrical methene containing carbethoxy groups rather than ethyl was unknown, it was prepared by the condensation



In this instance it was necessary to modify the usual methods for the preparation of methenes which failed due to the instability of this methene in solution.

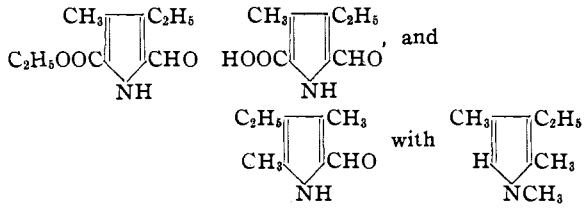
The three possible combinations of the N-methyl homologs of the pyrroles in this condensation failed to yield methenes. That this failure

(6) The authors are indebted to Dr. Maurice L. Huggins for suggesting and critically examining the possibility of the existence of H bridges.

(7) Fischer and Bartholomäus, *Z. physiol. Chem.*, **83**, 50 (1913); Fischer and Eismayer, *Ber.*, **47**, 2021 (1914); Fischer and Nenitzescu, *Ann.*, **443**, 123 (1925); Fischer, Halbig and Walach, *ibid.*, **452**, 287 (1927).

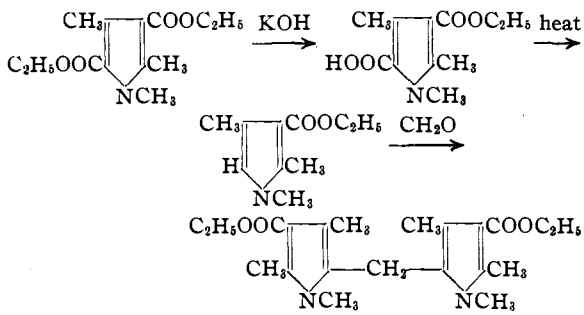
was due to a different type of reaction than that usually formulated will be shown in a separate communication.

To take advantage of the greater tendency toward methene formation exhibited by pyrroles containing only alkyl groups in the β-positions, the following combinations were tried



None of these yielded N-methyl methenes.

The failure of the aldehyde condensation led to an examination of the other general methods for methene synthesis. A di-N-methyldipyrrylmethane was prepared by the reactions



Neither the oxidation of this methane nor that of the hexamethyldiethylmethane mentioned earlier yielded a methene. The reactions of 1,2,4-trimethyl-3-carbethoxy and 1,2,4-trimethyl-3-ethylpyrroles with bromine and with formic acid again failed to yield methenes. Finally, attempts to methylate 3,5,3′,5′-tetramethyl-4,4′-dicarbethoxydipyrrylmethene were unsuccessful.

Our failure to obtain N-methylmethenes suggests the desirability of subjecting the various methene syntheses to careful scrutiny and commends to attention the possibilities of the synthesis of N-methylporphyrins by methods not involving the use of dipyrrylmethenes.

The authors are indebted to Mrs. G. Ware Wellwood for performing many of the microanalyses reported in this paper.

Experimental Part

2,4-Dimethyl-3,5-dicarbethoxypyrrole.[8]—The yield may be improved by adding sodium acetate to the zinc dust reduction to form a complex with zinc acetate and thus increase its solubility,[9] and by adding the solution of the nitroso compound to the mixture of zinc dust, sodium acetate, ethyl acetoacetate and glacial acetic acid instead of adding zinc dust to the other compounds; yield 75%.

1,2,4 - Trimethyl - 3,5 - dicarbethoxypyrrole.—Twenty-eight grams of sodium wire, 200 g. of 2,4-dimethyl-3,5-dicarbethoxypyrrole and two liters of toluene were heated with stirring for four hours on a steam-bath. The sodium salt of the pyrrole separated as a white curdy precipitate. Ninety cc. of freshly distilled dimethyl sulfate was then added dropwise and stirring and heating continued for another hour. The sodium methyl sulfate was filtered off and washed with toluene. The toluene was removed from the filtrate by steam distillation. On cooling the pyrrole crystallized out; yield 85–90%. The product may be recrystallized from methanol and water or from methanol alone by cooling with dry ice; m. p. 113–114°.

Anal. Calcd. for $C_{13}H_{19}O_4N$: C, 61.62; H, 7.56; N, 5.53. Found: C, 61.84; H, 7.95; N, 5.74.

As an alternative the sodium salt may be formed by the action of sodium tertiary amylate in tertiary amyl alcohol and subsequently methylated with dimethyl sulfate. The yield by this method was the same.

1,4 - Dimethyl - 2 - formyl - 3,5 - dicarbethoxypyrrole.—(a) Five grams of 2-formyl-3,5-dicarbethoxy-4-methylpyrrole was dissolved in a solution of 1.1 g. of potassium hydroxide in 11 cc. of methyl alcohol. Two and one-half cc. of dimethyl sulfate was added slowly below 50°. The mixture was allowed to stand for half an hour and cooled to crystallize the N-methyl aldehyde. The aldehyde was filtered off, washed with water and crystallized from methanol, m. p. 94°. This is the procedure of choice in quantity preparations.

(b) Twenty-five and three-tenths grams of 1,2,4-trimethyl-3,5-dicarbethoxypyrrole was dissolved in 127 g. of glacial acetic acid and 27 g. of sulfuryl chloride added slowly at 60°. The temperature was maintained for half an hour and the flask then cooled to 20° to permit crystallization of the aldehyde. Less pure product may be obtained by precipitating the mother liquor with water; m. p. 93°; mixed m. p. with aldehyde obtained in (a) 93°.

Anal. Calcd. for $C_{13}H_{17}O_5N$: C, 58.39; H, 6.41. Found: C, 58.34; H, 6.44.

1,2,4 - Trimethyl - 3 - carboxyl - 5 - carbethoxypyrrole.—The procedure was essentially that of Fischer and Walach[10] for the lower homolog. Twenty-five grams of 1,2,4-trimethyl-3,5-dicarbethoxypyrrole was added to 100 cc. of concd. sulfuric acid and the temperature kept below 30°: recovery 3 g.; yield 60% of the remainder; decomposition point 192°.

Anal. Calcd. for $C_{11}H_{15}O_4N$: C, 58.63; H, 6.71. Found: C, 58.99; H, 6.91.

1,2,4 - Trimethyl - 5 - carbethoxypyrrole.—The decarboxylation of the preceding compound was carried out as rapidly as possible in three times its weight of anhydrous glycerine;[11] yield 75%; m. p. 47°. The substance has a peculiar, sickening, sweetish odor.

(8) Hans Fischer, "Organic Syntheses," Vol. XV, 1935, p. 17; Winans and Adkins, THIS JOURNAL, **55**, 4167 (1933).

(9) Davidson and McAllister, *ibid.*, **52**, 507 (1930).

(10) Fischer and Walach, *Ber.*, **58**, 2820 (1925).

(11) Fischer, Berg and Schormüller, *Ann.*, **480**, 114 (1930).

Anal. Calcd. for $C_{10}H_{15}O_2N$: C, 66.25; H, 8.34. Found: C, 65.92; H, 8.34.

1,2,4 - Trimethyl - 3 - acetyl - 5 - carbethoxypyrrole.—(a) The best method for the preparation of this compound is the methylation of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole by the method given for 1,2,4-trimethyl-3,5-dicarbethoxypyrrole; yield 80%; m. p. 62° after recrystallization from ligroin.

(b) The preparation from 1,2,4-trimethyl-5-carbethoxypyrrole by the Friedel–Crafts reaction follows that of the lower homolog;[12] yield 25% after recrystallization; m. p. 60–61°; mixed m. p. with product from (a) 61°.

Anal. Calcd. for $C_{12}H_{17}O_3N$: C, 64.53; H, 7.67. Found: C, 64.46; H, 7.54.

1,2,4-Trimethyl-3-ethylpyrrole.—The procedure for preparing this from 1,2,4-trimethyl-3-acetyl-5-carbethoxypyrrole follows essentially that of Fischer, Baumann and Riedl.[13] The substance is sensitive to oxidation and should be protected by nitrogen; yield 55%; b. p. 93° at 23 mm.

Anal. Calcd. for $C_9H_{15}N$: C, 78.75; H, 11.02. Found: C, 77.85; H, 10.45.

(It appeared that this analytical discrepancy was due to the rapidity with which the substance oxidized during the weighing process.)

1,3,5,1',3',5' - Hexamethyl - 4,4' - diethyl - 2,2' - dipyrrylmethane.—Success in preparing this compound depends upon the absence of mineral acid. The acid necessary for condensation was supplied by using old formalin which had accumulated enough formic acid to give an acid reaction to litmus.

One gram of N-methylcryptopyrrole, 2 cc. of 95% ethyl alcohol and 0.5 cc. of 40% formalin solution were stirred together without warming. The methane separated in colorless crystals. The precipitate was filtered off, washed and crystallized from methanol. It was very sensitive to air and was dried in a vacuum and stored under nitrogen; m. p. 106°.

Anal. Calcd. for $C_{19}H_{30}N_2$: C, 79.65; H, 10.56. Found: C, 79.80; H, 10.67.

N-Methylmethylethylmaleic Imide.—(a) Two grams of 1,2,4-trimethyl-3-ethylpyrrole was suspended in a saturated aqueous solution of 8 g. of CrO_3 and 50 cc. of 20% sulfuric acid added drop by drop at 60°. The flask was kept at 70° for several hours with occasional stirring and rubbing of the resinous precipitate. The solution was cooled, extracted five times with ether, the extract washed with water, dilute soda solution and again with water, dried and distilled. The imide was a colorless oil; b. p. 215–220°.

(b) 1,3,5,1',3',5' - Hexamethyl - 4,4' - diethyl - 2,2' - dipyrrylmethane was oxidized according to the above procedure. N-methylmethylethylmaleic imide was isolated. When saponified according to the directions below and tested for ammonia the latter was found to be absent. CH_3NH_3Cl was isolated; m. p. 226–227°; mixed m. p. with CH_3NH_3Cl, 227°.

(c) One and four-tenths grams of methylethylmaleic imide was dissolved in 20 cc. of toluene and treated with 0.46 g. of sodium and then 2.52 g. of dimethyl sulfate according to the procedure for 1,2,4-trimethyl-3,5-dicarbethoxypyrrole. The toluene was removed by vacuum fractionation. The imide boiled at 215–221°.

Hydrolysis Procedure.—Two 50-cc. distilling flasks were connected through their side-arms with a small condenser. The first flask was provided with an ebullition tube, the second with a stopper containing a 12 in. length of 12 mm. glass tubing which dipped below a few cc. of distilled water in the flask. The imide was placed in the first flask with 20 cc. of normal sodium hydroxide solution and the apparatus tilted so that the condenser acted as a reflux during the hydrolysis. The solution was boiled for an hour, the apparatus tilted toward the second flask and the amine distilled slowly until most of the water had passed over. The liquid in the receiver was then tested for ammonia and methylamine by Thatcher's test.[14] No ammonia was found. A portion of the distillate was neutralized with hydrochloric acid and evaporated to dryness. A test portion of the residue was found to be completely soluble in absolute alcohol previously saturated with ammonium chloride. The residue was crystallized from hot absolute alcohol and ether; m. p. 227°; mixed m. p. with CH_3NH_3Cl, 227°.

1,2,4 - Trimethyl - 3 - ethyl - 5 - carbethoxypyrrole.—(a) This product may be prepared by the catalytic hydrogenation of 1,2,4-trimethyl-3-acetyl-5-carbethoxypyrrole in alcoholic solution with Raney's catalyst,[15] at 2500 pounds per sq. in. pressure and 150°. The pyrrole distilled at 124° at 2 mm. This is the method of choice in the preparation.

(b) The substance may be prepared by methylation of 2,4-dimethyl-3-ethyl-5-carbethoxypyrrole by the tertiary amylate method mentioned for 1,2,4-trimethyl-3,5-dicarbethoxypyrrole, b. p. 120–125° at 2 mm. Comparison of b. p. with product from (a) in the same apparatus shows them to be identical.

Anal. Calcd. for $C_{12}H_{19}O_2N$: C, 68.90; H, 9.09. Found: C, 68.65; H, 9.04.

3,5,4' - Tricarbethoxy - 4,3',5' - trimethyl - 2,2' - dipyrrylmethene.—Attempts to prepare this compound by any of the methods employed by Fischer for methene syntheses were unsuccessful. It was finally prepared by using cold ether as a solvent for the reaction and dry hydrogen chloride gas as a catalyst. The methene was so insoluble in ether that it crystallized out as rapidly as formed. It was then found that the earlier failures to obtain this methene were due to the fact that it decomposed when dissolved in alcohol or glacial acetic acid. In fact, this methene was not stable in any solvent which was investigated.

Two and five-tenths grams of 2-formyl-3,5-dicarbethoxy-4-methylpyrrole and 1.67 g. of 2,4-dimethyl-3-carbethoxypyrrole were dissolved with warming in 175 cc. of dry ether. The mixture was cooled to 10° and dry gaseous hydrogen chloride passed in for fifteen to twenty minutes. The solution was allowed to stand at 0° for several hours, the methene filtered off and washed with ether. Brilliant

(12) Fischer and Schubert, *Z. physiol. Chem.*, **155**, 102 (1926).

(13) Fischer, Baumann and Riedl, *Ann.*, **475**, 239 (1929).

(14) Mulliken, "Identification of Pure Organic Compounds," John Wiley & Sons, Inc., 1916, Vol. II, p. 20.

(15) Raney, THIS JOURNAL, **54**, 4116 (1932); Signaigo and Adkins, *ibid.*, **58**, 710 (1936).

yellow needles were obtained. The crystals changed color at 120° and sintered gradually as the temperature was raised. The substance could not be recrystallized satisfactorily. When dissolved in cold toluene and plunged quickly into dry ice, crystals separated which were less pure than the starting product. When this methene was boiled in alcohol it decomposed to give 2-formyl-3,5-dicarbethoxy-4-methylpyrrole, m. p. 124°, and a residue which has not been identified.

Anal. Calcd. for $C_{21}H_{27}O_6N_2Cl$: C, 57.44; H, 6.20. Found: C, 58.01, 57.95; H, 6.20, 6.65.

The analytical discrepancy indicates an impurity which differs from the aldehyde used, because this has less C and H than the methene, and which probably is not 2,4-dimethyl-3-carbethoxypyrrole since this should have been removed by the ether wash used. Hence we feel that the discrepancy needs further investigation.

The attempted condensations of aldehydes and α-unsubstituted pyrroles to give N-methylmethenes followed the directions given above. The combinations tried were 2-formyl-3,5-dicarbethoxy-4-methylpyrrole with 1,2,4-trimethyl-3-carbethoxypyrrole; 1,4-dimethyl-2-formyl-3,5-dicarbethoxypyrrole with 2,4-dimethyl-3-carbethoxypyrrole and with 1,2,4-trimethyl-3-carbethoxypyrrole; 1,2,4-trimethyl-3-ethylpyrrole with 2-formyl-3-ethyl-4-methyl-5-carbethoxypyrrole, with 2-formyl-3-ethyl-4-methyl-5-carboxylpyrrole, and with 2-formyl-3,5-dimethyl-4-ethylpyrrole. These condensations led to reddish or purple oils.

1,2,4 - Trimethyl - 3 - carbethoxy - 5 - carboxylpyrrole.—Twenty-six grams of potassium hydroxide was dissolved in 300 cc. of 95% alcohol and 105 g. of 1,2,4-trimethyl-3,5-dicarbethoxypyrrole added and refluxed for two and one-half hours. The solution was poured into cold water, talc added and filtered. The pyrrole acid was precipitated with hydrochloric acid, filtered off and dried, yield 90%.

Anal. Calcd. for $C_{11}H_{15}O_4N$: C, 58.63; H, 6.71. Found: C, 58.93; H, 7.18.

1,2,4 - Trimethyl - 3 - carbethoxypyrrole.—The preparation was similar to that of 1,2,4-trimethyl-5-carbethoxypyrrole; yield 75%; m. p. 57°; mixed m. p. with the 5-carbethoxy isomer, 39°. The substance has nearly the same sickening sweet odor as its isomer. Repeated recrystallizations raised the m. p. to 62°.

Anal. Calcd. for $C_{10}H_{15}O_2N$: C, 66.25; H, 8.34. Found: C, 66.40; H, 8.59.

1,3,5,1',3',5' - Hexamethyl - 4,4' - dicarbethoxy - 2,2' - dipyrrylmethane.—The procedure was similar to that of the corresponding 4,4'-diethylmethane except that hydrogen chloride catalyst was used and the mixture warmed. The yield was nearly quantitative, m. p. 151–152°.

Anal. Calcd. for $C_{21}H_{30}O_4N_2$: C, 67.33; H, 8.08. Found: C, 67.43; H, 8.45.

The preceding compound and its 4,4'-diethyl analog were treated with bromine in the usual manner for the preparation of methenes. Purple oils resulted from which no crystalline material could be isolated.

The method tried for the bromination of N-methyl pyrroles was essentially that of Fischer.[16] 1,2,4-Trimethyl-3-carbethoxypyrrole and 1,2,4-trimethyl-3-ethylpyrrole were tried and the products were purple oils.

The method tried for the condensation with formic acid was essentially that of Fischer and Zerweck.[17] The pyrroles used in the bromination were used in this condensation and again purple oils resulted.

3,5,3',5' - Tetramethyl - 4,4' - dicarbethoxydipyrrylmethene, obtained by the formic acid condensation of Fischer and Zerweck was treated with sodium in the same manner as with Knorr's pyrrole. A bright red precipitate separated. When dimethyl sulfate was added to this the precipitate dissolved and the toluene solution turned green. When a toluene solution of the methene was treated with a small amount of mineral acid and warmed a similar green color appeared. This decomposition was even more marked in glacial acetic acid. Every attempt to recrystallize a mineral acid salt of this compound led to more or less extensive decomposition. A few minutes' boiling in glacial acetic acid was sufficient to complete this decomposition. We intend to submit this reaction to further investigation to determine whether or not this behavior is typical of dipyrrylmethenes.

Summary

1. The theoretical limits of a new type of isomerism have been discussed.

2. A program has been outlined which is designed to test the possibility of the existence of this type of isomerism.

3. The preparation of a group of N-methylpyrroles to fit into this program has been reported.

4. The formaldehyde synthesis of dipyrrylmethanes has been modified to permit the preparation of a completely alkylated dipyrrylmethane.

5. A method has been described for obtaining a dipyrrylmethene not available by older methods.

6. Attempts to prepare N-methyldipyrryl methenes have been described.

7. Certain decompositions of dipyrrylmethenes have been reported.

BALTIMORE, MD. RECEIVED MARCH 4, 1936

(16) Fischer, *Sitz. ber. math. physik. Klasse Bayer. Akad. Wiss. München*, 410 (1915).

(17) Fischer and Zerweck, *Ber.*, **56**, 526 (1923).