CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SOUTHWESTERN AT MEMPHIS]

THE CHEMISTRY OF BIPYRRYLS. I. THE PREPARATION OF A 1,1′-UNSUBSTITUTED 2,2′-BIPYRRYL

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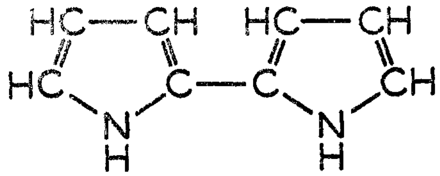
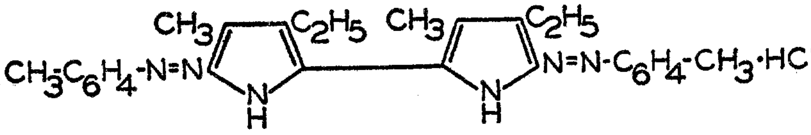
The present report describes the preliminary investigation of certain 2,2′-bipyrryls having no substituents (other than hydrogen) in the 1,1′-positions. The parent compound of this series, 2,2′-bipyrryl (I), has not been reported; there is reason to believe that it would be of low stability should its preparation be successful. Several reported compounds more or less closely related to I are discussed below.



I

The reaction of 3-ethyl-4-methylpyrrole with 4-methylbenzenediazonium chloride produced two compounds of unknown constitution one of which, on analytical evidence alone, was assigned the structure II (1). It seems probable that in the event of the formation of such a compound all three possible isomers resulting from the alternate orientations of the pyrrole nuclei would result. In view of the physical properties of the material a more likely structure might be that of a substituted 2-pyrryl-2-pyrrolenine salt.



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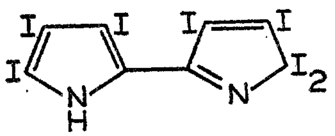

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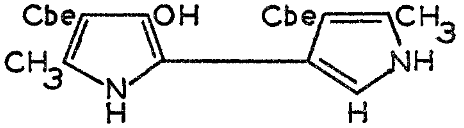

IV

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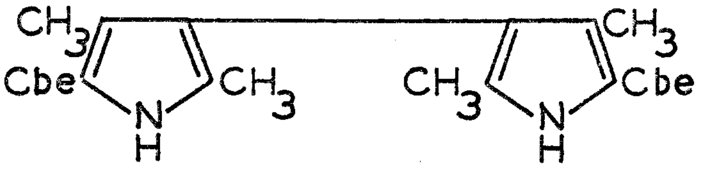
When pyrrylmagnesium bromide was treated with bromine at −15° and then with water (2), there was formed an unstable substance, believed to be 2-bromopyrrole, which on steam-distillation yielded another unstable compound which gave bromine analyses of 38.15, 38.22, 39.68% (compared with 37.86% for $C_8H_7BrN_2$) and was called "bromodipyrrole." This compound was too unstable for further characterization.

The treatment of pyrrole, 2-carboxypyrrole, or 2-formylpyrrole with hypoiodite (3) gave "heptaiododipyrryl" which was assigned the structure of heptaiodo-2-pyrryl-2′-pyrrolenine (III).



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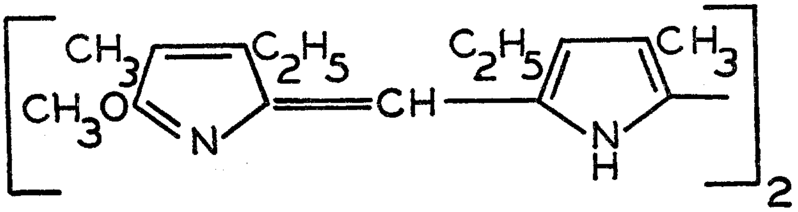


VI

From the reaction of 3-carbethoxy-4-hydroxy-2-methylpyrrole with concentrated hydrochloric acid (4) a compound was obtained which was believed to have the 2,3′-bipyrryl structure IV.

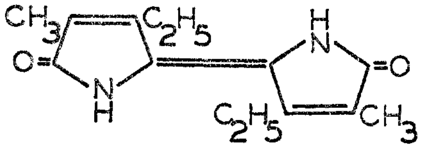
In the preparation of 2,4-dimethyl-5-carbethoxy-3-formylpyrrole (5) a side reaction product designated as "dimeric 2,4-dimethyl-5-carbethoxypyrrole" was isolated and assigned the 3,3′-bipyrryl structure V.

The partially reduced forms of I, 2-pyrryl-2′-pyrroline and 2-pyrroline-2′-pyrrolidine, have been prepared by ring condensation followed by reduction (6).

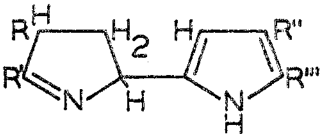
Using a Pd-$CaCO_3$ catalyst the appropriate 5-bromobipyrrylmethene was converted to a compound for which the structure VI was written which is thus a bi-dipyrrylmethene and may be considered as a complex derivative of (I) (7).

The reaction of 4-methyl-2-triacetoxymethyl-3-ethylpyrrolenine-5 with potassium hydroxide (8) yielded 3,3′-diethyl-4,4′-dimethyl-$\Delta^{2,2'}$-bipyrroline-5,5′-dione (VII), the quinone corresponding to a simply substituted I.

While the structure of "tripyrrole" is believed to contain some form of direct pyrrole-pyrrole linkages its structure is still uncertain. The "dipyrroles" formed by the action of acids on pyrroles have been shown (9) to be substituted 2-pyrryl-2′-(Δ^1-pyrrolines) (VIII).



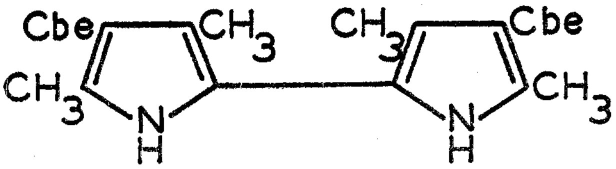
VII



VIII

The original object of this investigation was the preparation of 4,4′-dicarbethoxy-3,3′,5,5′-tetramethyl-2,2′-bipyrryl (IX). Three schemes were proposed for its synthesis:

A. The Ullmann reaction on 4-carbethoxy-2-iodo-3,5-dimethylpyrrole (X). This reaction was carried out under conditions involving variations of solvent, pressure, temperature, time of reaction, light, and reacting metal. Invariably the material isolated consisted of highly colored tars from which nothing recognizable could be obtained. The earlier report (2) of what was believed to be "bromodipyrrole" described a compound so unstable as not to permit accurate analysis. It thus seems possible that the simple 1,1′-unsubstituted 2,2′-bipyrryls lacking sufficient stabilizing groups are actually unstable. In the above case the two carbethoxy groups might have been expected to produce stabilization; apparently their influence was inadequate.

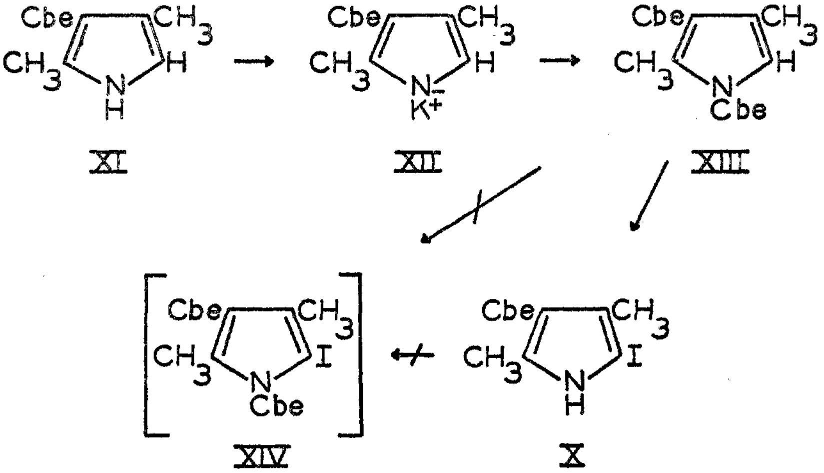


IX

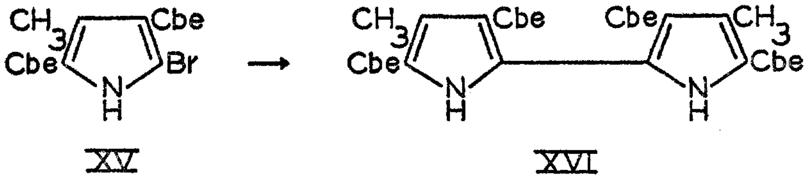
B. 3,5-Dicarbethoxy-2,4-dimethylpyrrole → 3-carbethoxy-5-carboxy-2,4-dimethyl-pyrrole → 3-carbethoxy-2,4-dimethylpyrrole (XI) → N-potassium salt of 3-carbethoxy-2,4-dimethylpyrrole (XII) → 1,3-dicarbethoxy-2,4-dimethylpyrrole (XIII) → 1,3-dicarbethoxy-5-iodo-2,4-dimethylpyrrole (XIV) → 1,1′,4,4′-tetracarbethoxy-3,3′,5,5′-tetramethyl-2,2′-bipyrryl → 4,4′-dicarbethoxy-1,1′-dicarboxy-3,3′,5,5′-tetramethyl-2,2′-bipyrryl → IX.

This series of reactions failed at the step requiring the conversion of XIII into XIV. On treatment of XIII with iodine, instead of the formation of the expected compound XIV, a new reaction took place involving iodination of the 2-position accompanied by the loss of the 1-carbethoxy group resulting in the formation of X. It seems possible that the 1-carbethoxy group was lost as a unit since there was no evidence of decarboxylation or decomposition and the yield of X was virtually quantitative.

C. Unsuccessful attempts were made to prepare 1,3-dicarbethoxy-5-iodo-2,4-dimethylpyrrole (XIV) (see above) by direct carbethoxylation of 4-carbethoxy-2-iodo-3,5-dimethylpyrrole (X).



The substitution of negative groups on the pyrrole nucleus or an alkyl or aryl group on the ring nitrogen produces a stabilizing effect on this heterocyclic system. Thus in the accompanying paper (10) a stable, resolvable 2,2′-bipyrryl resulted when both these conditions were satisfied. In an attempt to prepare a stable 1,1′-unsubstituted 2,2′-bipyrryl a tetracarbethoxy derivative suggested itself and the synthesis of such a compound was carried out successfully using the Ullmann reaction on 2-bromo-3,5-dicarbethoxy-4-methylpyrrole (XV) to yield 3,3′,5,5′-tetracarbethoxy-4,4′-dimethyl-2,2′-bipyrryl (XVI).



This compound was stable and exhibited a beautiful blue fluorescence in solution.

EXPERIMENTAL[2]

4-Carbethoxy-2-iodo-3,5-dimethylpyrrole (X). A solution was prepared by dissolving 4.22 g. (0.02 mole) of 3-carbethoxy-5-carboxy-2,4-dimethylpyrrole in 150 cc. of water containing 10.1 g. (0.12 mole) of sodium bicarbonate and 50 cc. of 95% ethanol. With stirring 50 cc. of a solution containing 5.08 g. (0.02 mole) of iodine dissolved in a water solution of potassium iodide was added as rapidly as decolorization took place. When all the I_3^- solution

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[2] All melting points are corrected.

had been added, the reaction mixture containing the partially precipitated 4-carbethoxy-2-iodo-3,5-dimethylpyrrole was diluted with water and filtered. After washing and drying the product melted 144–146° and weighed 5.50 g. (93.9%).

Reaction of 4-carbethoxy-2-iodo-3,5-dimethylpyrrole (X) *with copper*. The general procedure used was as follows: 4-carbethoxy-2-iodo-3,5-dimethylpyrrole was ground in a mortar with 1.5 times its weight of copper powder. A thermometer was used to stir the mixture as the temperature was raised slowly by means of a silicone heating-bath. When the temperature of the mixture and bath reached 145–150° a reaction took place accompanied by a temperature rise to 175–180° and considerable darkening. The reaction mixture was removed from the bath, cooled, and extracted with one of several solvents (ethanol, chloroform, benzene, ethyl acetate). The solvent was removed and attempts were made to purify the residue.

When the reaction was run below 145° only starting product was isolated. Previous to reaction an attempt was made to remove the oxygen by alternate application of a vacuum and of nitrogen; there was no lessening of decomposition. The reaction was run in boiling xylene or benzene with the same results. The presence or absence of light did not affect the reaction.

No solvent or combination of solvents could be found which would yield a crystalline product from the residue. Chromatography from a chloroform-isoöctane solution on calcium hydroxide failed to yield any crystalline material, though four colored fractions were separated (pink, greenish-yellow, purple, and deep purple or black). The first two of these were fluorescent.

Reaction of the iodopyrrole with powdered sodium metal in xylene produced the N-sodium salt of the iodopyrrole, from which the starting material could be regenerated.

The reaction was run using powdered silver and heated to 155°. The reaction mixture turned red, but only starting product was isolated.

1,3-Dicarbethoxy-2,4-dimethylpyrrole (XIII). This reaction was carried out in the apparatus described immediately above. To a solution of 20.4 g. (0.122 mole) of 3-carbethoxy-2,4-dimethylpyrrole in 150 cc. of dry toluene 4.77 g. (0.122 mole) of potassium was added. Gradually the reaction mixture was heated to the boiling point with continuous stirring. The resulting slurry of the pyrrole potassium salt was cooled in an ice-bath and a solution of 13.24 g. (0.122 mole) of ethyl chlorocarbonate in 35 cc. of dry toluene was added slowly. The temperature was kept between 5–10°. When the addition of the ethyl chlorocarbonate had been completed the reaction mixture was heated to 50° for 5 minutes and then cooled and filtered to remove the KCl (9.05 g.). After decolorizing with Norit the filtrate was concentrated under a vacuum, cooled in a Dry Ice-acetone bath, and filtered. Additional material was recovered by concentration of the mother liquor. The yield of 1,3-dicarbethoxy-2,4-dimethylpyrrole was 16.0 g. (54.8%) which melted 40–41°. On recrystallization at Dry Ice temperature from ethanol the melting point rose to 42°. The Ehrlich test for *alpha*-free pyrroles was positive.

Anal. Calc'd for $C_{12}H_{17}NO_4$: C, 60.23; H, 7.16.
Found: C, 60.30; H, 7.20.

Reaction of 1,3-dicarbethoxy-2,4-dimethylpyrrole (XIII) *with iodine*. To a solution of 15.0 g. (0.063 mole) of 1,3-dicarbethoxy-2,4-dimethylpyrrole in 50 cc. of methanol 10.6 g. (0.012 mole) of sodium bicarbonate was added. The mixture was heated to boiling and with stirring 16.0 g. (0.063 mole) of iodine in 125 cc. of methanol was added slowly. Upon completion of the iodine addition, the reaction mixture was refluxed 10 minutes, filtered with suction, and diluted carefully with excess water. The heavy floc of flesh-colored needles on drying melted 145–147°. On recrystallization from ethanol at Dry Ice temperature the material melted 146–148° and showed no depression with an authentic sample of 4-carbethoxy-2-iodo-3,5-dimethylpyrrole. The weight of the unrecrystallized material was 18.2 g. (99%).

Anal. Calc'd for $C_9H_{12}INO_2$: C, 36.87; H, 4.13.
Found: C, 37.51; H, 4.18.

Attempted N-carbethoxylation of 4-carbethoxy-2-iodo-3,5-dimethylpyrrole (X). This reaction was carried out in a 250-cc. 3-necked flask equipped with a stirrer, thermometer, condenser with drying tube, and Glascol heater. A solution of 12.6 g. (0.043 mole) of 4-carbethoxy-2-iodo-3,5-dimethylpyrrole in 125 cc. of sodium-dried toluene was heated to 60° and with stirring 1.68 g. (0.043 mole) of potassium was added. When the temperature reached 65° the potassium fragmented and the potassium salt of the pyrrole began to appear. After stirring for 2 hours at 70° the reaction mixture was cooled and the pyrrole potassium salt was filtered and washed with dry ether, taking care to always have the solid wet with ether. (This operation required considerable caution since the dry potassium salt may contain traces of potassium which is pryophoric in air.) The salt, wet with ether, was replaced in an identical reaction flask equipped as above but with a dropping-funnel added. The addition of a solution of 4.67 g. (0.043 mole) of ethyl chlorocarbonate in 25 cc. of sodium-dried toluene was begun. At the first drop a violent reaction took place which blew out the drying tube and thermometer. The reaction flask was then placed in an ice-salt bath and the addition of the ethyl chlorocarbonate was completed with no rise in temperature but was accompanied by a blackening of the reaction mixture. Nothing recognizable could be isolated from the reaction.

3,3′,5,5′-Tetracarbethoxy-4,4′-dimethyl-2,2′-bipyrryl (XVI). An intimate mixture of 2.0 g. (0.0066 mole) of 2-bromo-3,5-dicarbethoxy-4-methylpyrrole (XV) (11) and 3.0 g. of copper powder in a test tube was heated slowly in a silicone fluid bath. When the bath temperature reached 180° the temperature of the reaction mixture quickly rose to 210°. The bath was then raised to 210° and maintained at this temperature for ten minutes. On cooling the reaction mixture was extracted with six 15-cc. portions of boiling ethanol. The extract was decolorized with Norit, evaporated to 15 cc., and poured into an excess of water. The precipitated material upon two recrystallizations from ethanol-water weighed 0.8 g. (54%) and melted 178–179°. In ethanol or acetone solution this compound showed a strong blue fluorescence.

Anal. Calc'd for $C_{22}H_{28}N_2O_8$: C, 58.92; H, 6.29; $-OC_2H_5$, 40.19.
Found: C, 59.10; H, 5.96; $-OC_2H_5$, 39.7.

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SUMMARY

1. The preparation of a 1,1′-unsubstituted 2,2′-bipyrryl is described.
2. An unusual reaction involving 2-iodination and N-decarbethoxylation of a pyrrole derivative is reported.

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REFERENCES

(1) Grabowski and Marchlewski, *Ber.*, **47**, 2159 (1914).
(2) Hess and Wissing, *Ber.*, **48**, 1884 (1915).
(3) Pieroni, *Gazz. chim. ital.*, **51**, I, 47 (1921); Pratesi, *Atti. accad. Lincei*, **17**, 173 (1933).
(4) Benary and Silbermann, *Ber.*, **46**, 1363 (1913); Fischer and Loy, *Z. physiol. Chem.*, **128**, 75 (1923); Fischer and Heyse, *Ann.*, **439**, 236 (1924).
(5) Fischer and Kutscher, *Ann.*, **481**, 214 (1930).

(6) CRAIG, *J. Amer. Chem. Soc.*, **56**, 1144 (1934).
(7) FISCHER AND STACHEL, *Z. physiol. Chem.*, **258**, 121 (1939); see also FISCHER AND ASCHENBRENNER, *Z. physiol. Chem.*, **245**, 108 (1937).
(8) SIEDEL AND WINKLER, *Ann.*, **554**, 201 (1943).
(9) ALLEN, GILBERT, AND YOUNG, *J. Org. Chem.*, **2**, 227, 235 (1937).
(10) WEBB, *J. Org. Chem.*, **18**, following paper (1953).
(11) CORWIN, BAILEY, AND VIOHL, *J. Amer. Chem. Soc.*, **64**, 1267 (1942).