[Contribution from the Department of Chemistry of Southwestern at Memphis]

THE CHEMISTRY OF BIPYRRYLS. II. THE PREPARATION AND RESOLUTION OF A 1,1′-DISUBSTITUTED 2,2′-BIPYRRYL EXHIBITING RESTRICTED ROTATION

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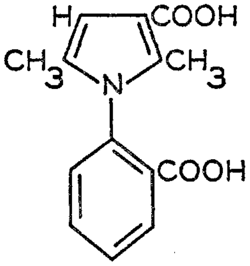
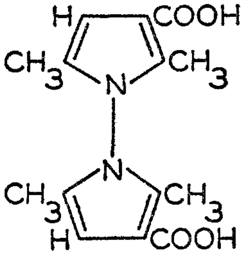
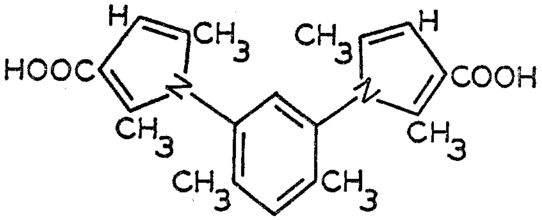
In the previous paper (1) the preparation of a 1,1′-unsubstituted 2,2′-bipyrryl was described. The present report concerns the preparation and resolution of a 1,1′-disubstituted 2,2′-bipyrryl exhibiting restricted rotation about the 2,2′-bond.



I



II

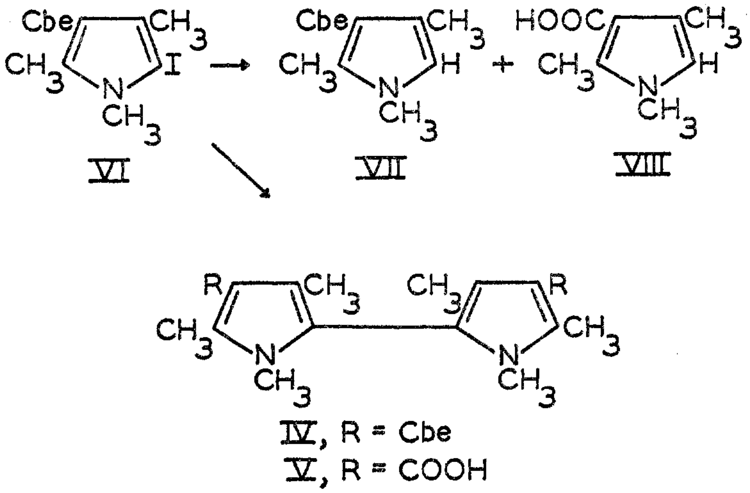


III

Three polycyclic systems containing pyrrole nuclei and exhibiting restricted rotation have been reported: I (2), II (3), and III (4). Each of these compounds was prepared by ring closure and each was resistant to racemization.

Two methods were investigated for the preparation of the completely substituted, stable 4,4′-dicarbethoxy-1,1′,3,3′,5,5′-hexamethyl-2,2′-bipyrryl (IV) and its acid (V) described here.

A. An attempt was made to produce ring coupling by reacting 4-carbethoxy-2-iodo-1,3,5-trimethylpyrrole (VI) with the Busch Pd-$CaCO_3$ catalyst in a manner analogous to that used by Fischer and Stachel (5). However, instead of ring coupling, dehalogenation took place accompanied by partial hydrolysis of the carbethoxy group yielding VII and VIII.



B. The preparation of the desired bipyrryl (IV) was accomplished in good yield by use of VI in the Ullmann reaction with copper powder. Prolonged refluxing of IV with alcoholic potassium hydroxide produced the corresponding bipyrryl acid, 4,4′-dicarboxy-1,1′,3,3′,5,5′-hexamethyl-2,2′-bipyrryl (V).

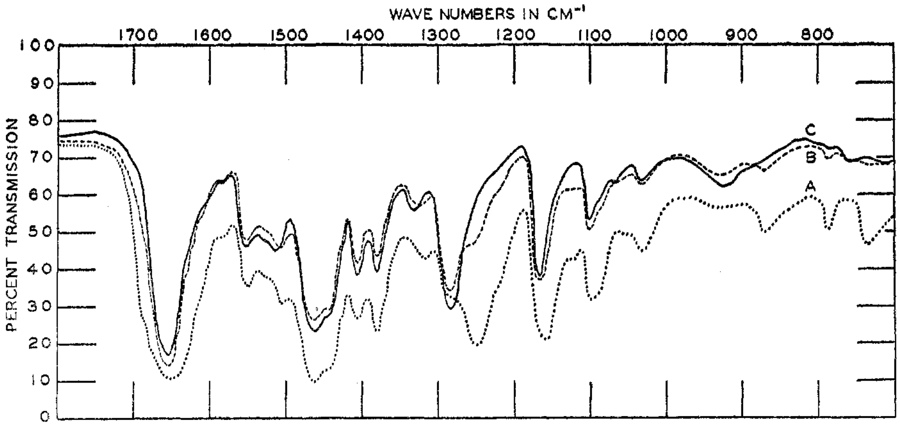


Fig. 1. Infrared Spectra of 4,4′-Dicarboxy-1,1′,3,3′,5,5′-hexamethyl-2,2′-bipyrryl (V): A, D-form; B, partially resolved L-form; C, racemic mixture. All spectra in Nujol mulls.

That the methyl groups of the bipyrryl acid (V) in the 1,1′- and the 3,3′-positions exhibit ample interference to restrict rotation may be seen from a drawing of the molecule made to scale (6) or by the use of models. Brucine was used in the resolution which yielded the pure D-form but only partially resolved L-form.

In the infrared spectra major differences occur between the racemate and the active forms of V between 1200 and 1300 cm.$^{-1}$ (Fig. 1). As expected, these differences are less pronounced in the case of the partially resolved L-form as compared to the racemate. Infrared absorption indicated racemization on melting of the active forms. These samples were examined as Nujol mulls, hence the vertical displacement due to variation in thickness.

EXPERIMENTAL[1]

3-Carbethoxy-5-iodo-1,2,4-trimethylpyrrole. This compound was prepared in 85–90% yield according to the procedure of Doak and Corwin (7) and, as these authors indicate, was obtainable in a colorless condition *only* by recrystallization at Dry-Ice temperatures from methanol or ethanol. The pure compound was considerably more stable than its 5-bromo analog.

Reaction of 4-carbethoxy-2-iodo-1,3,5-trimethylpyrrole (VI) *with Busch palladium catalyst.* A mixture of 2.0 g. (0.0065 mole) of 4-carbethoxy-2-iodo-1,3,5-trimethylpyrrole dissolved in 150 cc. of absolute methanol, 100 cc. of 5% potassium hydroxide solution in methanol, and 6.0 g. of Busch palladium catalyst (8) was refluxed gently for 24 hours. After the first 15 minutes the catalyst, originally tan in color, had changed to grey and remained thus. The warm solution was filtered and the catalyst was washed with methanol after which the filtrate was concentrated to 50 cc. and diluted to 500 cc. with water. The pink, waxy crystals (platelets) were filtered by suction and upon recrystallization from alcohol-water weighed 0.4 g. and melted at 51–53°. This compound gave a strong Ehrlich reaction and a mixture melting point with an authentic sample of 3-carbethoxy-1,2,4-trimethylpyrrole (VII) showed no depression. The methanol-water filtrate from the above crystals was acidified with 6 *N* hydrochloric acid to $p\text{H}\sim 2$. On standing in the refrigerator overnight the cloudy solution yielded fine crystals (needles) which were filtered with suction and upon recrystallization from ethanol-water weighed 0.1 g. This base-soluble compound gave a strong Ehrlich reaction and thus was presumably 3-carboxy-1,2,4-trimethylpyrrole (VIII).

The above reaction was carried out using 0.38 g. (0.0015 mole) of 2-bromo-4-carbethoxy-1,3,5-trimethylpyrrole and again 3-carbethoxy-1,2,4-trimethylpyrrole (0.05 g.) was obtained. No effort was made to isolate the corresponding free acid from the reaction.

4,4'-Dicarbethoxy-1,1',3,3',5,5'-hexamethyl-2,2'-bipyrryl (IV). An intimate mixture of 8.0 g. (0.026 mole) of 4-carbethoxy-2-iodo-1,3,5-trimethylpyrrole (VI) and 12.0 g. of copper powder[2] in a test tube was heated slowly in a silicone fluid bath. When the bath temperature reached 160° the temperature of the mixture had risen to 225° after which it fell slowly to the temperature of the bath which was maintained at 200° for 50 minutes with frequent stirring. Upon cooling the reaction mixture was extracted with ten 15-cc. portions of boiling ethanol. The extract, after decolorization with Norit, was evaporated to 15 cc. and cooled in a Dry Ice-acetone bath until crystallization was complete. The filtered crystals, washed with a small amount of cold ethanol, weighed 2.75 g. (58.6%) and melted 110–111°. After two recrystallizations from ethanol at Dry Ice temperatures the melting point rose to 117.5–118°.

Anal. Calc'd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; $—OC_2H_5$, 25.00; M. W., 360.44.
Found: C, 66.54; H, 7.50; $—OC_2H_5$, 24.9; M. Wt. (Rast), 364.

4,4'-Dicarboxy-1,1',3,3',5,5'-hexamethyl-2,2'-bipyrryl (V). During a period of one hour 10.0 g. (0.178 mole) of potassium hydroxide dissolved in 30 cc. of water was added to a

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[1] All melting points are corrected.

[2] No. 44, Venus, Natural Copper, U. S. Bronze Powder Works, Inc., 220 W. 42nd Street, New York 18, N.Y.

refluxing solution of 6.15 g. (0.017 mole) of 4,4′-dicarbethoxy-1,1′,3,3′,5,5′-hexamethyl-2,2′-bipyrryl (IV) dissolved in 40 cc. of 95% ethanol. After refluxing had continued for 48 hours the hot solution was decolorized with Norit and ethanol was removed on the steam cone under a water-pump vacuum. The evaporation was accompanied by much frothing. The solid residue was cooled in an ice-salt bath and acidified to *p*H 2 with 6 *N* hydrochloric acid. After 30 minutes the mixture was centrifuged; the solid dicarboxylic acid, washed four times by centrifugation with ice-water, was dried in an oven at 80° and weighed 4.96 g. (92.5%). After recrystallization from dioxane and drying under an oil-pump vacuum at 90° for two hours this compound turned dark when put in a bath previously heated to 280° and sublimed rather sharply at 290–291°.

Anal. Calc'd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; Neut. equiv., 152.17.

Found: C, 62.97; H, 6.62; Neut. equiv., 152.0.

Resolution of 4,4′-dicarboxy-1,1′,3,3′,5,5′-hexamethyl-2,2′-bipyrryl (V). A solution of 8.97 g. (0.023 mole) of brucine in 200 cc. absolute methanol was brought to a gentle boil and with stirring a suspension of 3.45 g. (0.011 mole) of 4,4′-dicarboxy-1,1′,3,3′,5,5′-hexamethyl-2,2′-bipyrryl (V) in 100 cc. of absolute methanol was added slowly with continuous stirring. The mixture was boiled for ten minutes, allowed to cool to room temperature, and then placed in an ice-bath for four hours. After suction filtration and drying in a vacuum desiccator over silica gel the crystalline material weighed 8.0 g. After three recrystallizations from absolute methanol the material weighed 2.79 g. and the melting point was constant, 217–218° (bath pre-heated to 210°), as was the rotation.

Rotation. Dibrucine salt of D-acid: 0.1000 g. made up to 10.00 cc. in pyridine gave $[\alpha]_D^{25}$ −82.00°.

D-*4,4′-Dicarboxy-1,1′,3,3′,5,5′-hexamethyl-2,2′-bipyrryl* (V). To a suspension of 2.634 g. of the above dibrucine salt in 60 cc. of water 2.7 cc. of conc'd hydrochloric acid was added slowly with vigorous stirring. After 30 minutes the precipitated dicarboxylic acid was filtered, washed with a small amount of cold water, and dried in a vacuum desiccator. The dried acid, weighing 0.775 g., was recrystallized three times from dioxane and dried under an oil-pump vacuum at 50° for two hours. This material sublimed at 289–290° in a bath pre-heated to 280°.

Rotation. D-acid: 0.1000 g. made up to 10.00 cc. in pyridine gave $[\alpha]_D^{25}$ +37.00°. No mutarotation was observed on heating to 50° in pyridine solution. Infrared absorption indicated racemization on melting.

The filtrate containing the brucine•HCl from the regeneration of the above D-acid was made basic with sodium hydroxide and the precipitated brucine was filtered, water-washed, and dried under an oil-pump vacuum at 50° for two hours. This material melted 173–174° and weighed 1.885 g. (Theory for dibrucine salt of D-acid, 1.898 g.).

L-*4,4′-Dicarboxy-1,1′,3,3′,5,5′-hexamethyl-2,2′-bipyrryl* (V). (*a*) All of the filtrates from the dibrucine salt of the D-acid were combined, evaporated under a water-pump vacuum to 20 cc., and cooled in ice. The crystals thus obtained, which melted 191–193° with decomposition, after three recrystallizations from absolute methanol weighed 2.68 g. and had the constant m.p. 196–197° with decomposition when put in a bath pre-heated to 190°.

Rotation. Monobrucine salt of impure L-acid: 0.1000 g. made up to 10.00 cc. in pyridine gave $[\alpha]_D^{25}$ −82.5°.

To a suspension of 2.116 g. of the above monobrucine salt in 40 cc. of water 2.0 cc. of conc'd hydrochloric acid was added slowly with stirring. After one-half hour the precipitated dicarboxylic acid was filtered, washed with a small amount of dilute hydrochloric acid, then with water, and dried in a vacuum desiccator. The acid, recrystallized twice from dioxane and dried in a vacuum desiccator, weighed 0.355 g. and melted with decomposition and sublimation at 289–290° when put in a bath pre-heated to 280°.

Rotation. Impure L-acid: 0.1000 g. made up to 10.00 cc. in pyridine gave $[\alpha]_D^{25}$ −5.0°.

The filtrate from the above impure L-acid containing brucine·HCl was neutralized with vigorous stirring; the precipitated brucine was filtered, washed with water, and dried in an oil-pump vacuum at 50° weighed 1.190 g. (Theory for monobrucine salt of the diacid, 1.194 g.).

(*b*) In a second attempt to obtain the pure L-acid the filtrates from the above brucine salts were acidified and the diacid thus obtained was combined with that above. A solution of 1.902 g. (0.00482 mole) of brucine in dioxane was added to 0.733 g. (0.00241 mole) of the diacid dissolved in 40 cc. of dioxane. The solution was evaporated to dryness under a water-pump vacuum on the steam-bath and the syrupy residue was taken up in absolute methanol. After a few minutes crystals began to form which on filtration weighed 1.180 g. (the dibrucine salt of the D-acid).

The filtrate from the above, concentrated and cooled in ice, yielded 0.568 g. of crystalline material. Extraction of these crystals once with boiling absolute ethyl acetate failed to dissolve an appreciable amount of material. After three recrystallizations from absolute methanol the melting point was 216–217° in a bath pre-heated to 210°.

Rotation. Dibrucine salt of impure L-acid: 0.1000 g. made up to 10.00 cc. in pyridine gave $[\alpha]_D^{25}$ $-75.0°$.

The free diacid was isolated from the dibrucine salt as described above and after two recrystallizations from absolute methanol melted 288–290° with decomposition when put in a bath pre-heated to 280°.

Rotation. Impure L-acid: 0.1000 g. made up to 10.00 cc. in pyridine gave $[\alpha]_D^{25}$ $-12.0°$.

The samples for infrared absorption were prepared as a solid suspension in mineral oil.

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SUMMARY

1. A 1,1′-disubstituted 2,2′-bipyrryl exhibiting restricted rotation has been synthesized and resolved.

2. The infrared absorption spectra of the D-, partially resolved L-, and racemic forms of this compound have been reported.

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