

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

**THE STEREOCHEMISTRY OF N-PHENYLPYRROLES.  
THE PREPARATION AND RESOLUTION OF N-2-CARBOXY-  
PHENYL-2,5-DIMETHYL-3-CARBOXYPYRROLE. XIII<sup>1</sup>**

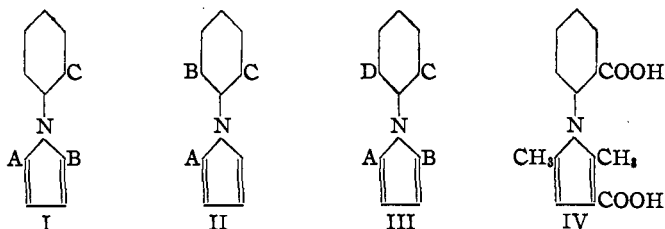
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RECEIVED DECEMBER 15, 1930

PUBLISHED JANUARY 12, 1931

The search for the presence of stereoisomerism in certain substituted molecules containing rings of an aromatic or semi-aromatic type is a natural development from the study of diphenyl compounds. Such a field, the study of which is being undertaken in this Laboratory, includes compounds in the series of the phenylpyridines, dipyrindyls, phenylpyrroles, phenylpyrazoles, etc. The difficulty of synthesis, however, is a severe hindrance to the rapid development of the study of these types. Only recently has the first dicyclic compound other than a diphenyl been found in which this type of isomerism exists. The compound was a phenylquinone.<sup>1a</sup> In all of the researches connected with the various substances just mentioned the attachment of one ring to the other has been attempted always through carbon linkages.

A preliminary study has now been made to determine whether certain properly substituted dicyclic compounds with carbon-nitrogen linkages between the rings might not show similar isomerism. A class of such compounds which has interesting possibilities is the N-phenylpyrroles represented by the general structures (I), (II) and (III). This communi-



cation describes a compound which belongs to Type I. It is N-2-carboxyphenyl-2,5-dimethyl-3-carboxypyrrole (IV), prepared by condensing anthranilic acid with 3-carbethoxy-2,5-hexadione (prepared from chloroacetone and acetoacetic ester) and then saponifying. Resolution was effected by means of the brucine salt. The same remarkable difference in solubility between the two diastereoisomeric salts exists as in the salts from previously resolved diphenyl compounds.

<sup>1</sup> For the preceding papers in this series see (a) Shildneck and Adams, *THIS JOURNAL*, **53**, 343 (1931); (b) Stoughton and Adams, *ibid.*, **52**, 5263 (1930).

<sup>2</sup> This communication is a portion of a thesis submitted by L. H. Bock in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

The active forms do not racemize upon boiling for eight hours in ethyl alcohol. They are, however, essentially completely racemized upon boiling for twenty-four hours in 0.1 *N* sodium hydroxide solution.

If the usual explanation of the phenomenon in the diphenyl series is applied here, it may be said that there is restricted rotation between the benzene ring and the pyrrole ring due to the interference of the ortho substituted groups. Whether the same conditions for the appearance of the phenomenon hold as in the diphenyl series is to be determined. However, the possibility must not be overlooked that in this molecule the optical activity may be dependent, not upon the restricted rotation but upon the character of the nitrogen atom or it may be dependent on a combination of the two. Experiments which are now under way and which will be reported soon should indicate with considerable certainty whether this latter explanation is likely, and at that time a detailed discussion of the theoretical possibilities will be given.

Based on the results just described, optical activity may also be expected in properly substituted *N*-phenyltetrazoles, *N*-phenylpyrazoles, *N*-phenylpyrroldiazoles, etc., as well as in the ortho substituted dicyclic compounds with the two nitrogens attached to each other as in *N,N*-dipyrroles, *N,N*-dipyrzoles, *N,N*-ditetrazoles and *N,N*-dipyrroldiazoles, etc. Representatives of these classes are being prepared.

### Experimental

**3-Carbethoxy-2,5-hexadione.**—This compound was previously prepared by Weltner<sup>8</sup> from monochloroacetone and acetoacetic ester. In a 1-liter, three-necked flask equipped with a mercury-sealed stirrer, reflux condenser and dropping funnel were placed 260 g. of acetoacetic ester and 25 g. of sodium. The mixture was stirred at room temperature until all of the sodium had dissolved. This required about twenty-four hours. Then 250 cc. of dry ether was added and 99 g. of monochloroacetone was slowly added. Stirring was continued for eighteen hours. The reaction mixture was filtered, washed with water and extracted with ether. The product distilled at 95–105° (3 mm.). The yield was 96 g. (48% of the theoretical amount).

***N*-2-Carboxyphenyl-2,5-dimethyl-3-carboxypyrrole.**—A solution of 18.6 g. of 3-carbethoxy-2,5-hexadione and 13.7 g. of anthranilic acid in 100 cc. of absolute ethyl alcohol was refluxed for one hour. The reaction mixture was then refluxed for fifteen minutes with alcoholic sodium hydroxide, filtered, cooled and acidified with dilute hydrochloric acid. Eight grams of crude product precipitated. It was purified by crystallization from one liter of ethyl acetate containing a little alcohol; m. p. 224.5–225.5°. It is soluble in alcohol, ether and acetic acid but only slightly soluble in ethyl acetate and chloroform.

*Anal.* Calcd. neut. equiv.: 129.6. Found: 128.6. Calcd. for  $C_{14}H_{13}O_4N$ : C, 64.84; H, 5.0. Found: C, 65.33; H, 5.1.

**Resolution of *N*-2-Carboxyphenyl-2,5-dimethyl-3-carboxypyrrole.**—A solution of 15.5 g. of brucine in 400 cc. of dry ethyl acetate was added hot to a suspension of 10 g. of *N*-2-carboxyphenyl-2,5-dimethyl-3-carboxypyrrole in 400 cc. of hot ethyl acetate. A

<sup>8</sup> Weltner, *Ber.*, 17, 67 (1884).

clear solution resulted from which the brucine salt precipitated when the side of the beaker was rubbed with a stirring rod. The mixture was cooled and filtered, yielding 12.8 g. of salt which gave  $[\alpha]_D -37^\circ$ . On concentrating the filtrate, 10 g. of salt of  $[\alpha]_D +12^\circ$  was obtained. The first fraction was recrystallized from 200 cc. of absolute alcohol to constant rotation. The more soluble fraction was recrystallized from ethyl acetate.

*l*-Salt.—0.1137 g. made up to 15 cc. with chloroform at  $20^\circ$  gave  $\alpha_D -0.68^\circ$ ;  $l = 2$ ;  $[\alpha]_D^{20} -44.9^\circ$ ; m. p. 231–232° (dec.).

*Anal.* Calcd. for  $C_{37}H_{39}O_3N_3$  (monobrucine salt): C, 67.96; H, 6.0. Found: C, 67.74; H, 6.1.

*d*-Salt.—0.1551 g. made up to 15 cc. with chloroform at  $20^\circ$  gave  $\alpha_D +0.28^\circ$ ;  $l = 2$ ;  $[\alpha]_D^{20} +13.5^\circ$ ; m. p. 175–180° (dec.).

*Anal.* Calcd. for  $C_{37}H_{39}O_3N_3$ : C, 67.96; H, 6.0. Found: C, 67.71; H, 6.1.

*d*- and *l*-N-2-Carboxyphenyl-2,5-dimethyl-3-carboxypyrroles.—The salts were decomposed by shaking in a separatory funnel with dilute hydrochloric acid and ether. The acid went into the ether layer and was obtained by evaporating to dryness. The acids were crystallized from ethyl acetate to constant rotation.

*l*-Acid.—0.1349 g. made up to 15 cc. with absolute alcohol at  $20^\circ$  gave  $\alpha_D -0.49^\circ$ ;  $l = 2$ ;  $[\alpha]_D^{20} -27.2^\circ$ ; m. p. 203–204°.

*d*-Acid.—0.1753 g. made up to 15 cc. with absolute alcohol at  $20^\circ$  gave  $\alpha_D +0.63^\circ$ ;  $l = 2$ ;  $[\alpha]_D^{20} +27.0^\circ$ ; m. p. 202–204°.

**Racemization Experiments.**—About 0.3 g. of *l*-compound in 50 cc. of absolute alcohol was boiled for eight hours. No change in initial rotation took place. In boiling glacial acetic acid, the rotation dropped to nearly zero in one hour but there was obviously decomposition occurring which probably accounted for this. Only a gram could be recovered from the heated solution.

A solution of 0.2107 g. of *l*-acid in 25 cc. of 0.1 *N* sodium hydroxide gave an initial rotation of  $\alpha_D -0.39^\circ$  ( $[\alpha]_D^{20} -23.1$ ). After eighteen hours' standing at room temperature, no change occurred. Upon boiling for twenty-four hours, the rotations were as follows: 1 hr.,  $\alpha_D -0.39^\circ$ ; 4 hrs.,  $\alpha_D -0.31^\circ$ ; 8 hrs.,  $\alpha_D -0.26^\circ$ ; 24 hrs.,  $\alpha_D -0.03^\circ$ . Upon acidification racemic acid was obtained, m. p. 224–225°.

### Summary

The preparation and resolution of N-2-carboxyphenyl-2,5-dimethyl-3-carboxypyrrole has been described.

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### NOTES

**The Reaction between Dichloro-arsines and Secondary Aromatic Amines.**—Lewis and Stiegler [THIS JOURNAL, 52, 4164 (1930)] appear to have overlooked work already published on this subject.

Burton and Gibson [J. Chem. Soc., 464 (1926)] having shown that the reaction between phenyldichloro-arsine and diphenylamine did not yield 10-phenyl-5,10-dihydrophenarsazine but 10-chloro-5,10-dihydrophenarsazine according to the equation

