

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

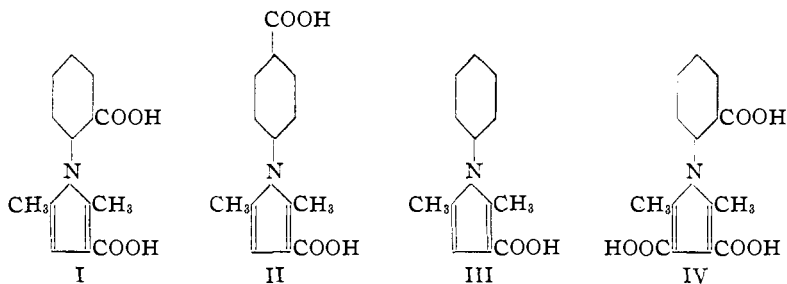
STEREOCHEMISTRY OF PHENYL PYRROLES. XIX¹BY L. H. BOCK² AND ROGER ADAMS

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The resolution of *N*-(2-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole³ into its enantiomorphs may be explained on the same basis as properly substituted diphenyls. On the other hand, as was pointed out, it is conceivable that this might be an example of a molecule containing an asymmetric nitrogen atom.

Several analogous compounds have now been studied in order to determine what conditions may be necessary for the existence of optical activity.



N-(4-Carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (II) and *N*-(3-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (III) were synthesized. It was impossible to resolve either and as a consequence it would appear likely that optical activity in the *o*-carboxyphenyl derivative is dependent, in part at least, on the presence of the ortho substituent in the phenyl group. If asymmetry is due to the nitrogen atom, it is improbable that moving the same substituent from the ortho to the meta or para position would so markedly affect its properties. From these preliminary results it might be concluded that conditions similar to those necessary in diphenyl molecules must exist in the phenyl pyrroles in order to obtain resolution.

In the communication describing a pair of optically active *N,N'*-dipyrrolys, a brief discussion of the possibilities for stereoisomerism in phenyl pyrroles and dipyrrolys was given on the assumption that the two rings in each of these molecules were not coaxial or in other words on the assumption that the nitrogen atom had a more or less fixed tetrahedral structure. Under such conditions, with interfering groups to prevent free

¹ For previous papers see Hill and Adams, *THIS JOURNAL*, **53**, 3453 (1931); Stanley and Adams, *ibid.*, **53**, 2364 (1931); Chang and Adams, *ibid.*, **53**, 2353 (1931).

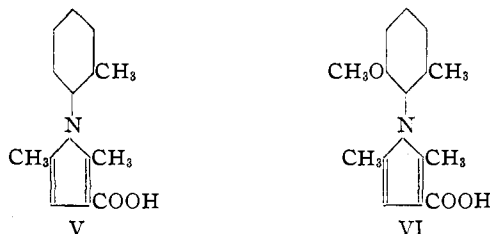
² This communication is in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

³ Bock and Adams, *THIS JOURNAL*, **53**, 374 (1931).

rotation between the rings, optical images should exist when only one ring is asymmetrically substituted. A molecule of this type has been prepared, *N*-(*o*-carboxyphenyl)-2,5-dimethyl-3,4-dicarboxypyrrole (IV). It could not be resolved. This is a further indication that the optical isomerism in phenyl pyrroles probably resembles closely that in the diphenyl series.

The *N*-(4-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (II) and the *N*-(3-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (III) were made by condensation, respectively, of *p*-aminobenzoic acid and *m*-aminobenzoic acid with 3-carbethoxy-2,5-hexadione. The *N*-(*o*-carboxyphenyl)-2,5-dimethyl-3,4-dicarboxypyrrole (IV) was readily formed from anthranilic acid and diacetylsuccinic ester.

In the course of this investigation *N*-(*o*-tolyl)-2,5-dimethyl-3-carboxypyrrole (V) and *N*-(2-methyl-6-methoxyphenyl)-2,5-dimethyl-3-carboxypyrrole (VI) were prepared but on account of the weakness of the acid character of each, stable salts could not be made.



Experimental

***N*-(4-Carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (II).**—A mixture of 35 g. of 3-carbethoxy-2,5-hexadione,³ 25.8 g. of *p*-aminobenzoic acid and 150 cc. of absolute alcohol was refluxed eleven hours. The *p*-aminobenzoic acid was not completely soluble at the start but gradually dissolved as the reaction progressed and was all in solution after about three hours. The resulting ester was saponified by adding a slight excess of sodium hydroxide to the solution and refluxing for one hour. The alkaline solution was treated with norite and poured slowly with stirring into 1 liter of ice water containing hydrochloric acid. The crude acid which precipitated was purified by crystallization from 2.5 liters of 95% alcohol. Two crystallizations yielded 14.5 g. of pure acid melting at 277–280° (corr.). The yield was 30% of the theoretical amount.

Anal. Calcd. neut. equiv.: 129.6. Found: 130.4. Calcd. for $C_{14}H_{13}O_4N$: C, 64.84; H, 5.06. Found: C, 64.99; H, 5.14.

Attempts to Resolve *N*-(4-Carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (II).—The monobrucine salt was prepared by adding a solution of 1.58 g. of brucine in 400 cc. of dry ethyl acetate to a suspension of 1.036 g. of acid in 200 cc. of absolute alcohol. The solution was boiled until all the acid dissolved. On standing, 1.3 g. of crystalline salt separated which had a specific rotation of -9.58° in absolute alcohol. On concentrating the mother liquor, 1 g. of salt with specific rotation of -10.7° was obtained. The first fraction of salt was decomposed with dilute hydrochloric acid and the free acid, dissolved in 0.8% sodium bicarbonate, was optically inactive.

Anal. Calcd. for $C_{37}H_{39}O_8N_3$: C, 67.96; H, 6.02. Found: C, 67.57; H, 6.14.

The monostrychnine salt was prepared by dissolving 3.32 g. of acid and 4.28 g. of strychnine in 150 cc. of absolute alcohol. An equal volume of dry ethyl acetate was added. The first fraction of crystals gave a specific rotation of -4.3° in pyridine and gave an optically inactive acid on decomposition.

Anal. Calcd. for $C_{35}H_{35}O_6N_3$: C, 70.79; H, 5.95. Found: C, 70.05; H, 6.05.

N-(3-Carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (III).—*m*-Aminobenzoic acid and 3-carbethoxy-2,5-hexadione were condensed by the procedure followed in the preparation of N-(4-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole. The acid was purified by two crystallizations from ethyl acetate containing a little alcohol and melted at $229-233^\circ$ (corr.). The yield was 15% of the theoretical.

Anal. Calcd. neut. equiv.: 129.6. Found: 130.2. Calcd. for $C_{14}H_{13}O_4N$: C, 64.84; H, 5.06. Found: C, 65.46; H, 5.22.

Attempts to Resolve N-(3-Carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole.—The monobrucine salt was prepared by dissolving 3.65 g. of acid and 5.56 g. of brucine in a mixture of 400 cc. of ethyl acetate and 200 cc. of absolute alcohol. Three fractions of crystalline salt totaling 7 g. were obtained with specific rotations in chloroform of -5.1 , -5.8 and -5.1° , respectively.

Anal. Calcd. for $C_{37}H_{35}O_8N_3$: C, 67.96; H, 6.02. Found: C, 68.31; H, 6.07.

The monostrychnine salt was prepared by dissolving 3.44 g. of acid and 4.44 g. of strychnine in a mixture of 200 cc. of ethyl acetate and 400 cc. of absolute alcohol. Two fractions totaling 6.7 g. were obtained with specific rotations of -1.41 and -1.43° .

Anal. Calcd. for $C_{35}H_{35}O_6N_3$: C, 70.79; H, 5.95. Found: C, 71.42; H, 5.98.

Upon decomposition, neither of these salts gave active acids.

N-(2-Carboxyphenyl)-2,5-dimethyl-3,4-dicarboxypyrrole (IV).—A mixture of 38 g. of diacetylsuccinic ester,⁴ 20 g. of anthranilic acid and 70 cc. of absolute alcohol was refluxed for ten hours on a steam-bath. The resulting ester was saponified with 30 g. of potassium hydroxide in 50 cc. of water and the free acid was precipitated by pouring the aqueous alkaline solution slowly with stirring into 500 cc. of ice water containing 60 cc. of concentrated hydrochloric acid. The acid was purified by crystallizing from 50% alcohol and melted at $237-238^\circ$. The yield was 14 g. or 31% of the theoretical amount.

Anal. Calcd. for $C_{15}H_{13}O_6N$: C, 59.38; H, 4.32. Found: C, 59.40; H, 4.56.

Attempts to Resolve N-(2-Carboxyphenyl)-2,5-dimethyl-3,4-dicarboxypyrrole.—The monostrychnine salt was prepared by dissolving 0.909 g. of acid and 1.002 g. of strychnine in 50 cc. of absolute alcohol and adding an equal volume of benzene. Three fractions of crystalline salt totaling 1.6 g. were obtained whose specific rotations were $+1.5$, $+1.5$ and 0.0° in absolute alcohol.

Anal. Calcd. for $C_{36}H_{35}O_8N_3$: C, 67.79; H, 5.54. Found: C, 65.58; H, 5.28.

The first fraction was decomposed with 0.5 *N* sodium hydroxide and the free acid obtained was optically inactive.

The monocinchonine salt was prepared by dissolving 1.818 g. of acid and 1.764 g. of cinchonine in 50 cc. of absolute alcohol and adding an equal volume of ethyl acetate. Five fractions of crystals totaling 2.7 g. were obtained whose specific rotations were $+80.7$, $+80.5$, $+82.9$, $+79.8$ and $+71.6^\circ$ in absolute alcohol. The first fraction was decomposed with 0.5 *N* sodium hydroxide and the free acid recovered was optically inactive.

Anal. Calcd. for $C_{34}H_{35}O_7N_3$: C, 68.31; H, 5.91. Found: C, 67.96; H, 5.97.

N-(*o*-Tolyl)-2,5-dimethyl-3-carboxypyrrole (V).—A mixture of 11 g. of 3 carb-

⁴ Harrow, *Ann.*, 201, 144 (1881).

ethoxy-2,5-hexadione and 6.2 g. of *o*-toluidine was heated on an oil-bath at 130–150° for two and one-half hours. The reaction mixture was then refluxed for an hour with an excess of alcoholic potash and poured into cold dilute hydrochloric acid. The crude acid was purified by crystallizing from 95% alcohol; m. p. 184.5–185.5° (corr.).

Anal. Calcd. neut. equiv.: 229. Found: 227.2. Calcd. for $C_{14}H_{16}O_2N$: C, 73.32; H, 6.60. Found: C, 73.36; H, 6.68.

N-(2-Methyl-6-methoxyphenyl)-2,5-dimethyl-3-carboxypyrrole (VI).—The procedure followed was the same as that used in the preparation of N-(*o*-tolyl)-2,5-dimethyl-3-carboxypyrrole. 2-Methyl-6-methoxyaniline was prepared by the method of Gibson.⁵ The product was purified by crystallization from 95% alcohol and melted at 198–199° (corr.). The yield was 26% of the theoretical.

Anal. Calcd. neut. equiv.: 259. Found: 256.7. Calcd. for $C_{18}H_{17}O_3N$: C, 69.46; H, 6.61. Found: C, 69.58; H, 6.71.

Summary

1. Unlike the N-(2-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole, N-(3-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole and the N-(4-carboxyphenyl)-2,5-dimethylcarboxypyrrole could not be resolved.
2. It was also impossible to resolve N-(2-carboxyphenyl)-2,5-dimethyl-3,4-dicarboxypyrrole.
3. A discussion of the optical isomerism in phenyl pyrroles is given.

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

STUDIES IN THE CHLOROPHYLL SERIES.

VII. EVIDENCE AS TO STRUCTURE FROM MEASUREMENTS OF ABSORPTION SPECTRA

BY J. B. CONANT AND S. E. KAMERLING

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The synthesis of a variety of porphyrins by Fischer has shown the structure of this class of compounds. However, the relation between the porphyrins and chlorophyll *a* and *b* has not yet been definitely established. Willstätter expressed as his final opinion the probability that a very drastic chemical change was involved in the transition from chlorophyll and its near relatives (the phaeophorbides, chlorins and rhodins) to the porphyrins. Much milder methods of forming porphyrins from chlorophyll derivatives are now known and indicate a close connection between the two classes. The results of the investigation of chlorophyll in this Laboratory have led us to write structural formulas for chlorophyll derivatives which contain a dihydro porphyrin ring or its equivalent.¹ In this paper we shall present a certain number of physical facts which we believe strongly support our formulation.

⁵ Gibson, *J. Chem. Soc.*, 123, 1273 (1923).

¹ Paper V, *THIS JOURNAL*, 53, 2382 (1931).