

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

STEREOCHEMISTRY OF DIPYRIDYLS. PREPARATION AND RESOLUTION OF 2,4,2',4'-TETRACARBOXY-6,6'-DIPHENYL-3,3'-DIPYRIDYL. XX^{1,2}

BY E. H. WOODRUFF AND ROGER ADAMS

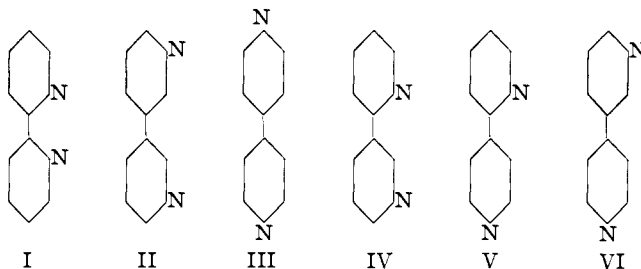
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The extension of the study of optical isomerism in certain substituted diphenyls to other binuclear ring systems has already been accomplished in certain cases, notably the N-phenylpyrroles, the N,N'-dipyrrolys, and the phenylquinones. However, attempts to obtain optically active compounds with a phenyl and a heterocyclic ring linked through a —C—C— linkage have thus far met with failure.

Steele and Adams³ and Lions⁴ have reported several unsuccessful attempts to resolve a —C—C— linked phenylpyridine. In spite of this fact it still seemed probable that with correctly selected groups in the *o*-positions, especially if all four positions are substituted, compounds might be found which could be resolved.

In this communication the study of a substituted dipyridyl is reported. There are six types of dipyridyls containing —C—C— linkage. The unsubstituted compounds are all known.⁵



If such molecules are analogous to diphenyl compounds, it might be anticipated that resolvable compounds of Type I and possibly of Types IV and V might not exist unless, perhaps, the nitrogen atoms were converted to quaternary ammonium groups.

A compound of the general type (II) has been prepared and resolved into optically active isomers. It is 2,4,2',4'-tetracarboxy-6,6'-diphenyl-

¹ This communication is an abstract of a thesis submitted by E. H. Woodruff in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

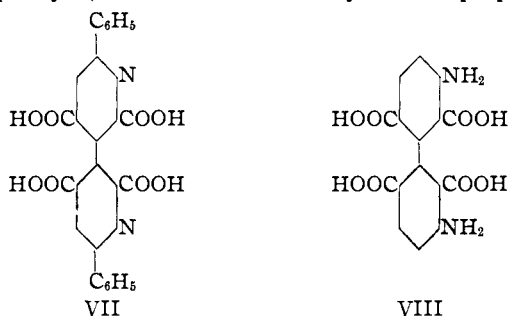
² The previous papers in this field are: Bock and Adams, *THIS JOURNAL*, **53**, 3519 (1931); Hill and Adams, *ibid.*, **53**, 3453 (1931).

³ Steele and Adams, *ibid.*, **52**, 4528 (1930).

⁴ Lions, *ibid.*, **53**, 1176 (1931).

⁵ C. R. Smith, *THIS JOURNAL*, **46**, 414 (1924).

3,3'-dipyridyl (VII). The active forms have rotations, $[\alpha]_D +6.1^\circ$, $[\alpha]_D -5.9^\circ$, and readily racemize upon warming in alcohol solution. It would appear, then, that the resistance to free rotation between the rings is very slight. It is probable that the interfering effect of two of the carboxyl groups is partially diminished due either to the smaller size of the ions found because of the presence of the basic nitrogen, or to the electrical characteristics of the ions or to the distortion of the forces on account of the internal neutralization of the carboxyl and the nitrogens. It is quite probable, moreover, that the character of a pyridine ring as regards conditions necessary for resolution of phenylpyridines and dipyridyls is different from that of benzene. Such a dipyridyl as has been described in this communication is quite analogous to a diphenyl of the formula 2,6,2',6'-tetracarboxy-3,3'-diaminodiphenyl (VIII) which has not yet been prepared. By past

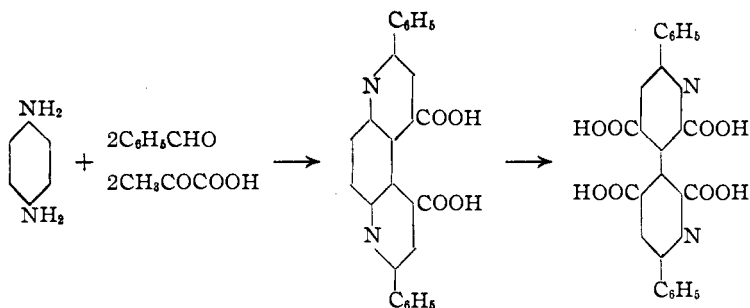


experience it would be expected that any ortho-tetracarboxydiphenyl with the two rings asymmetrically substituted but without other complicating factors should be relatively stable to racemization. However, in the diamino derivative the interfering effect of the two carboxyls adjacent to the two amines might be lessened to such an extent that the active compound would racemize readily.

The 2,4,2',4'-tetracarboxy-6,6'-diphenyl-3,3'-dipyridyl was synthesized by the following reactions. *p*-Phenylenediamine was condensed with benzaldehyde and pyruvic acid to 1,10-dicarboxy-3,8-diphenyl-4,7-phenanthroline. Although the exact structure of this compound was not determined, the conclusion that both nitrogen rings closed toward each other in the position indicated is supported by the results of previous investigators,⁶ who have proved that the unsubstituted phenanthroline made from *p*-phenylenediamine by the Skraup synthesis has the pyridine rings closed on the same side of the benzene ring. Moreover, the other isomeric phenanthroline could hardly be expected to oxidize to a tetrabasic acid.

Upon oxidation of the phenanthroline with potassium permanganate, the tetracarboxydipyridyl was obtained and resolved through the di-

⁶ Döbner and Ferber, *Ann.*, **281**, 16 (1894).



brucine salt. The chief difficulty involved was the isolation of the product due to the fact that the phenanthroline and tetracarboxydipyridyl are both acidic in character and rather similar in solubility.

Experimental

1,10-Dicarboxy-3,8-diphenyl-4,7-phenanthroline.—To 55 g. of *p*-phenylenediamine dissolved in 1 liter of boiling 95% alcohol in a 2-liter beaker was added 106 g. of benzaldehyde. The solution was then allowed to cool slightly until the Schiff base started to separate in the form of green-golden plates. The solution was then reheated to boiling and 88 g. of freshly prepared pyruvic acid was added with stirring over a period of five minutes in 10-cc. amounts. The reaction mixture boils violently so that the addition of pyruvic acid should not be too rapid. The solution, now deep red in color, was evaporated on a hot-plate to a total volume of 300–400 cc., when it was poured into a hot solution consisting of 60 g. of potassium hydroxide in 1500 cc. of distilled water. The solution was further evaporated until the volume reached about 1000 cc. in order that all of the alcohol would be removed. Then 1 liter of water was added and the solution was allowed to cool and stand. The by-product separated as a tar which solidified when cool. The solution was then filtered through norite. (This solution can now be used without further purification for the oxidation subsequently described.)

The isolation of the substituted phenanthroline was accomplished by heating the solution to 80–90° and acidifying with dilute hydrochloric acid. The product separated immediately in a crystalline condition and was filtered. If the solution was acidified when cold, the phenanthroline precipitated in an amorphous condition and was filtered and dried only with difficulty. The yield was 90–110 g. (42–50%).

Purification was accomplished by redissolving in a liter of hot potassium hydroxide solution (containing 40 g. of solid potassium hydroxide), filtering and reprecipitating with hydrochloric acid while hot. After cooling and filtering, the product could be crystallized from alcohol as follows. The dried material was dissolved in 300 cc. of hot 95% alcohol and filtered. It was then cooled in ice and salt and a small amount of material separated. The major portion did not appear until cooled to the temperature of a carbon dioxide–ether mixture. The product from alcohol is a deep brick red after it is dried and finely divided; yield 42 g. It may also be recrystallized from water, from which it separates as a bright scarlet material. The melting point is 250.5–251.5°, with decomposition.

Anal. Calcd. for $C_{26}H_{18}O_4N_2$: C, 74.26; H, 3.84; N, 6.66. Found: C, 74.20; H, 4.13; N, 6.68.

The di-silver salt of this compound was also prepared. A small amount of the acid (0.5–1.0 g.) was dissolved in 25 cc. of water containing a few drops of concentrated aqueous ammonia. The solution was then boiled to expel the excess ammonia and fil-

tered into a hot aqueous solution of silver nitrate. The di-silver salt separated as a yellow flocculent precipitate which was filtered with suction, washed with hot water and then with hot acetone.

Anal. Calcd. for $C_{28}H_{14}O_4N_2Ag_2$: Ag, 34.04. Found: Ag, 33.60.

2,4,2',4'-Tetracarboxy-6,6'-diphenyl-3,3'-dipyridyl.⁷—A solution of 21 g. of 1,10-dicarboxy-5,8-diphenyl-4,7-phenanthroline in 6 g. of potassium hydroxide, dissolved in 1 liter of water, was placed in a 2-liter beaker. Cracked ice was added to cool the solution to 10–15°, at which point a solution of 30 g. of potassium permanganate in 400 cc. of hot water was added with rapid stirring. This caused the temperature of the solution to rise to 20–25°. If the oxidation was carried out below this temperature, the manganese oxides formed did not coagulate properly and made filtration difficult. The solution was allowed to stand for one hour, after which time it was heated on a steam cone to coagulate further the oxides of manganese. After standing, the oxides settled and about one-half of the liquid could be decanted before filtration.

The filtered solution was placed in a large porcelain evaporating dish and was acidified with concentrated nitric acid to Congo red paper. The solution was then evaporated to dryness on a steam cone and the crude acids were extracted from the salt with acetone. The acetone solution, after filtration, was evaporated to dryness and the last traces of solvent removed in a vacuum desiccator. The dry product was boiled with 300 cc. of ethyl acetate and the hot solution filtered into 900 cc. of petroleum ether (b. p. 65–110°).

The precipitate was filtered with suction and partially dried by allowing the air to pass through for about fifteen minutes. This solid was then redissolved in 100 cc. of boiling ethyl acetate and the procedure repeated. This was again done, using about 50 cc. of ethyl acetate. This series of precipitations serves to remove the phenanthroline, which is only slightly soluble in ethyl acetate.

The removal of the last traces of solvent can be accomplished by a final drying in an Abderhalden dryer over phosphorus pentoxide at a temperature of 100° (water). About 7.5 g. of product was obtained as a light yellow powder, which decomposes without melting at 181°.

Anal. (Micro). Calcd. for $C_{28}H_{16}O_8N_2$: C, 64.44; H, 3.33; N, 5.78. Found: C, 64.13, 64.24; H, 3.51, 3.41; N, 5.16.

Resolution of 2,2',4,4'-Tetracarboxy-6,6'-diphenyl-3,3'-dipyridyl.—Two methods of resolution were used. The first was more extensively studied but the second proved much the simpler of the two.

First Method.—A solution of 4.84 g. (0.01 mole) of the tetracarboxydipyridyl in 200 cc. of ethyl acetate and a solution of 7.88 g. (0.02 mole) of brucine in 200 cc. of ethyl acetate were mixed together in a 2-liter beaker. Sufficient ethyl acetate was then added to dissolve almost completely the brucine salt. The hot solution was filtered, cooled and the precipitated salt filtered out by means of a Gooch crucible. About 0.5 g. was usually obtained.

Rotation. 0.2205 g. made up to 50 cc. with chloroform at 20° gave $\alpha_D -0.02 \pm 0.01^\circ$; $l = 1$; $[\alpha]_D^{25} -4.9^\circ$.

This precipitate was extracted several times with 100-cc. portions of hot ethyl acetate, but neither the residue nor the salt which separated on cooling showed any change in rotation.

The filtrate from the 0.5 g. of salt from the original solution was then concentrated and various fractions as they precipitated were filtered. This was continued until a volume of 50 cc. was reached when no more salt could be obtained in a solid condition

⁷ Skraup and Vortmann, *Monatsh.*, 4, 583 (1883).

upon cooling the solution. These intermediate fractions were worked up for less soluble and more soluble salt by the process just discussed.

Upon evaporating the 50 cc. to dryness and removing the last traces of solvent by suction, the more soluble salt was obtained in a dry powdery form. Generally less than a gram was obtained.

Rotation. 0.1136 g. made up to 20 cc. with chloroform at 20° gave $\alpha_D -0.20 \pm 0.01^\circ$; $l = 1$; $[\alpha]_D^{25} -35.8^\circ$.

Second Method.—To a solution of 9.682 g. (0.02 mole) of the acid in 200 cc. of ethyl acetate was added 7.88 g. (0.02 mole) of brucine in 100 cc. of ethyl acetate. A precipitate (8.7 g.) was obtained which decomposed without melting at 202–207°. It was purified by boiling with ethyl acetate to dissolve any more soluble salt which had adhered.

Rotation. 0.1400 g. made up to 50 cc. with chloroform at 20° gave $\alpha_D -0.01 \pm 0.01^\circ$; $l = 1$; $[\alpha]_D^{25} -3.5^\circ$.

Upon the addition of another 7.88 g. (0.02 mole) of brucine in 100 cc. of ethyl acetate, 1.9 g. more of precipitate was obtained which apparently was a less soluble form.

Rotation. 0.1623 g. made up to 50 cc. with chloroform at 20° gave $\alpha_D -0.046 \pm 0.01^\circ$; $l = 1$; $[\alpha]_D^{25} -5.6^\circ$.

The solution was then evaporated to 50 cc., whereupon 14 g. of salt had precipitated.

Rotation. 0.1916 g. made up to 20 cc. with chloroform at 20° gave $\alpha_D -0.19 \pm 0.01^\circ$; $l = 1$; $[\alpha]_D^{25} -19.8^\circ$.

The last 50 cc. was evaporated to dryness and 3 g. of more soluble salt was obtained.

It turns brown at 155–160° and melts with decomposition at 180–184°.

Rotation. 0.1500 g. made up to 20 cc. with chloroform at 20° gave $\alpha_D -0.26 \pm 0.01^\circ$; $l = 1$; $[\alpha]_D^{25} -34.7^\circ$.

By extracting the 14 g. of intermediate fraction with 50-cc. portions of the ethyl acetate, 1.5 g. of the more soluble salt was readily obtained having $[\alpha]_D^{25} -35^\circ$.

Anal. Calcd. for $C_{22}H_{18}N_6O_{16}$: N, 6.69. Found: for less soluble salt, N, 6.61; for more soluble salt, N, 6.66.

d and *l*-2,2'-4,4'-tetracarboxy-6,6'-diphenyl-3,3'-dipyridyl.—Three grams of the salt $[\alpha]_D^{25} -5.0^\circ$ was triturated in a small porcelain mortar with ice-cold, 5% hydrochloric acid, filtered and washed with distilled water. After partially drying, the procedure was repeated. The acid was then taken up in ice-cold, very dilute sodium hydroxide and shaken three times with 100-cc. portions of chloroform. The solution was filtered into cold dilute hydrochloric acid. (The procedure occupied about twenty minutes up to this point.) The free acid separated and was filtered and washed with distilled water and dried over phosphorus pentoxide *in vacuo* at room temperature. About 0.8 g. of the acid (entirely free from brucine) was recovered from the 3 g. of salt.

Rotation. 0.0896 g. made up to 20 cc. with acetone at 20° gave $\alpha_D +0.035 \pm 0.01^\circ$; $l = 1$; $[\alpha]_D^{25} +7.8^\circ$. 0.1628 g. made up to 20 cc. with 95% alcohol at 20° gave $\alpha_D +0.05 \pm 0.01^\circ$; $l = 1$; $[\alpha]_D^{25} +6.1^\circ$.

The same procedure was followed with the more soluble salt. The yield of free acid was less from this fraction.

Rotation. 0.0677 g. made up to 20 cc. with 95% alcohol at 20° gave $\alpha_D -0.04 \pm 0.01^\circ$; $l = 2$; $[\alpha]_D^{25} -5.9^\circ$.

Anal. Calcd. for $C_{28}H_{16}N_2O_8$: N, 5.78. Found: for +6.1° acid, N, 5.16; for -5.9° acid, N, 5.08.

Racemization Tests.—0.3705 g. made up to 50 cc. with 95% alcohol at 20° gave $\alpha_D +0.04 \pm 0.01^\circ$; $l = 1$; $[\alpha]_D^{25} +5.4^\circ$. The solution was allowed to stand at room temperature for twenty hours ($T = 33-35^\circ$). $\alpha_D +0.02 \pm 0.01^\circ$; $[\alpha]_D^{25} +2.7^\circ$.

The solution was then boiled for fifteen minutes, after which the rotation was 0.

Due to the deep color of the sodium salt, no rotation could be observed on account of the extreme dilution which was necessary before light would pass through the tube.

Summary

1. 2,4,2',4'-Tetracarboxy-6,6'-diphenyl-3,3'-dipyridyl has been prepared by the oxidation of 1,10-dicarboxy-3,8-diphenyl-4,7-phenanthroline. This in turn was prepared by the condensation of *p*-phenylenediamine with benzaldehyde and pyruvic acid.

2. The dipyridyl was resolved through the brucine salt. The active acid was readily racemized by warming for a short time in ethyl alcohol.

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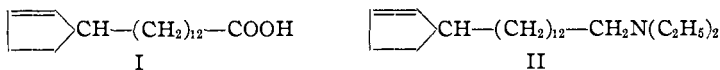
THE PREPARATION OF VARIOUS OMEGA-CYCLOHEXYL ALKYL AMINES AND THEIR BACTERICIDAL ACTION TO MYCOBACTERIUM LEPRAE. XXII¹

BY GERALD H. COLEMAN AND ROGER ADAMS

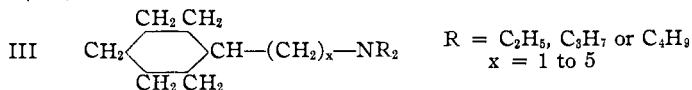
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In one of the earlier papers² describing the preparation and bactericidal properties of various aliphatic acids, it was demonstrated in the case of chaulmoogric acid (I) that the carboxyl group could be replaced by a $-\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ group and the product (II) still had bactericidal properties.



The present investigation involved the synthesis of a series of ω -cyclohexyl-alkyl tertiary amines of varying molecular weight and of the general formula (III).



These compounds correspond essentially to the series of acids described in earlier papers.

The bacteriological study was made with the same strain of *Mycobacterium leprae* used with the acids. The amines were made into the hydrochloride salts and tested in the same manner as the sodium salts of the acids.^{1b} The table (I) of results is given below.

The conclusions are very definite. The bactericidal value is dependent, in part at least, on molecular weight just as in the acids. It is obvious

¹ For the last three papers in this series see (a) Stanley, Coleman, Greer, Sacks and Adams, *J. Pharmacol.* (June, 1932); (b) Stanley and Adams, *THIS JOURNAL*, **54**, 1548 (1932); (c) Greer and Adams, *ibid.*, **52**, 2540 (1930).

² Sacks and Adams, *ibid.*, **48**, 2395 (1926).