Summary

Iodine and thiocyanogen numbers for unsaturated compounds of various types have been determined by the Hanus solution (one and two hours) and Kaufmann solution (forty-seven hours), respectively. The results are discussed in connection with the general question of the effect of negative groups in the vicinity of the ethylene bond in hindering the addition of the halogen and halogenoid. Such a hindrance is evident. The effect decreases with the distance of the negative group from the ethylenic linkage. Ester formation does not materially alter the negativity of carboxyl.

Thiocyanogen is much less reactive than iodine. At least thirty hours should be allowed for this reaction. Longer time of reaction than forty-eight hours leads to uncertainty of results due to progressive deterioration of the reagent.

In the case of alcohols high values may be found due to reaction with the alcohol group in addition to the reaction of saturation.

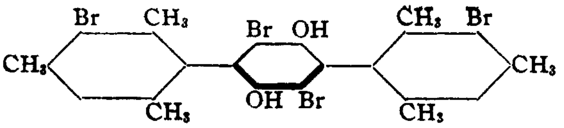
BROOKLYN, N. Y. RECEIVED JUNE 20, 1934

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

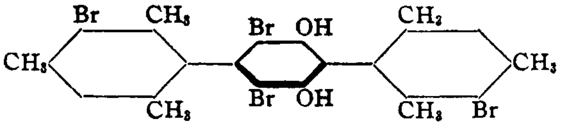
Stereochemistry of Diphenyls. XXXVI. Preparation and Resolution of Certain Substituted Dipyrrylbenzenes[1]

BY CHIN CHANG[2] AND ROGER ADAMS

By the isolation of the *cis* and *trans* forms of certain properly substituted diphenylbenzenes it was demonstrated that molecules containing two points of restricted rotation of the diphenyl type existed in the expected two diastereoisomeric forms. The *cis* and *trans* 3,6-di-(3-bromo-2,4,6-trimethylphenyl) - 2,5 - dibromohydroquinone (I and II) represent such a pair of diastereoisomers.[3]



I. *cis*



II. *trans*

Structural models clearly demonstrate that the *cis* form is racemic and the *trans* form meso, but all the attempts to confirm this by resolution of the *cis* and non-resolution of the *trans* resulted in failure, due, presumably, to the difficulty of introducing satisfactory salt-forming groups.

The investigation of compounds with two points of restricted rotation has been extended to the dipyrrylbenzenes. Previous results have established that phenylpyrroles may exist optically active and that the necessary conditions of substitution conform essentially to those in the diphenyl series. Moreover, it was demonstrated that the nitrogen atom plays no role in the optical activity. The preparation and study of various dipyrrylbenzenes, therefore, present several points of interest: (1) isolation of diastereoisomeric salts would confirm the correctness of the previous generalizations made concerning molecules with two points of restricted rotation; (2) dipyrrylbenzenes containing salt-forming groups can readily be produced and it would, therefore, be possible by a study of the resolution to distinguish the *cis* and *trans* modifications; (3) the *m*-dipyrrylbenzenes should be just as readily synthesized as the *p*-derivatives, whereas no method is available for the preparation of *m*-diphenylbenzene derivatives.

It is of interest that dependent on the type of substitution and whether the molecules are *p*- or *m*-diphenyl or dipyrrylbenzenes, the *cis* form may be either meso or racemic and the *trans* form either meso or racemic. Such possibilities have been discussed in detail elsewhere,[1] so that it is merely necessary to mention here that in a dipyrrylbenzene molecule of type III and IV the *cis* form is meso and the *trans* form racemic, whereas in the type V and VI the *cis* form is racemic and the *trans* form meso.

Compounds V and VI correspond exactly from a stereochemical viewpoint to Compounds I and II in the *p*-diphenylbenzene series.

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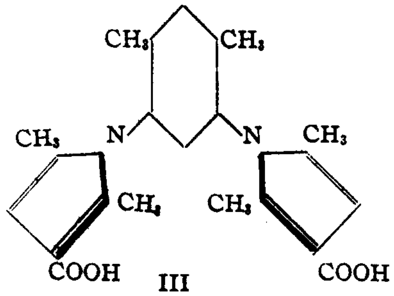
[1] For the previous paper see Chien and Adams, THIS JOURNAL, 56, 1787 (1934). Also Adams and Yuan, *Chem. Rev.*, 12, 261 (1933).

[2] Submitted as part of a thesis for the Degree of Doctor of Philosophy at the University of Illinois.

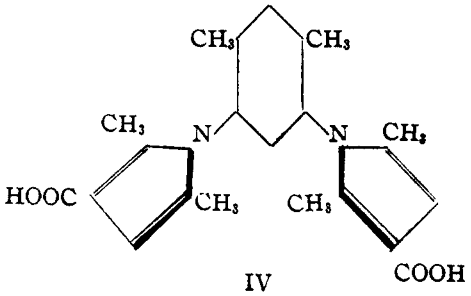
[3] Shildneck and Adams, *ibid.*, 53, 343, 2203 (1931); Browning and Adams, *ibid.*, 52, 4098 (1930).



III

cis-meso

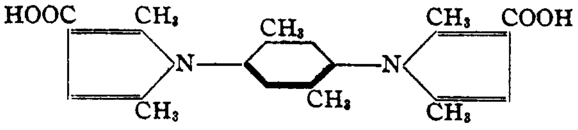
(carboxyls on same side of benzene ring)



IV

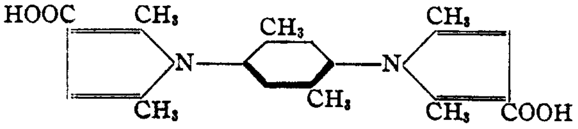
trans-racemic

(carboxyls on opposite sides of benzene ring)



V

cis-racemic



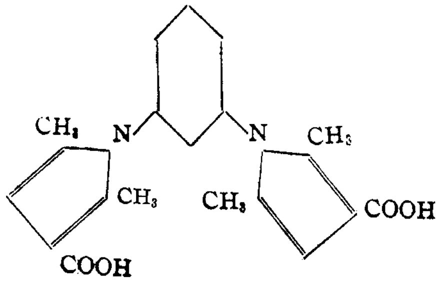
VI

trans-meso

On the assumption that in either the *m*- or *p*-series the less soluble higher-melting form is *trans*, and the more soluble lower-melting form is *cis*, the less soluble stereoisomer in the *m*-series (IV) should be resolvable and the more soluble (III) not resolvable, whereas in the *p*-series the less soluble stereoisomer (VI) should not be resolvable and the more soluble stereoisomer (V) resolvable. These predictions have been essentially confirmed experimentally. The two diastereoisomers (III and IV) as well as V and VI were readily synthesized and isolated in pure condition. Moreover, IV was readily resolved and III could not be. Unfortunately, attempts at resolution of V and VI were failures, since with either isomer salts with alkaloids could not be formed. In all cases but one, regardless of the nature of alkaloid and solvent, the free acid and not the salt separated from solution, due to the slight solubility of the free acid. The brucine salt in dioxane separated as a jelly.

The active forms of IV are very resistant to racemization. Boiling pyridine for several days caused no change in optical rotation and only by boiling in alkali for over four days was a partial racemization noticed.

The 1,3-di-(2,5-dimethyl-3-carboxypyrryl)-benzene was also synthesized but, as might be expected, did not give two diastereoisomeric forms due presumably to lack of restricted rotation.



Experimental

The method of preparation of the dipyrrylbenzenes corresponded to that used for the synthesis of phenylpyrroles except that the proper aromatic diamine and two moles of 3-carboethoxy-2,5-hexadione were used. In the case of the *m*-compound no attempt was made to separate the stereoisomeric esters produced in the initial reaction. The crude mixture was hydrolyzed and the acids fractionated apart. With the *p*-compound, the two esters were separated, though it was a simpler procedure to isolate the pure acids from each other.

4,6-Dinitro-1,3-dimethylbenzene.—G. Errera and R. Maltese[4] described the nitration of 1,3-dimethylbenzene to give a mixture of 4,6- and 2,4-dinitro derivatives. Conditions for improving the yield of the 4,6-dinitro-1,3-dimethylbenzene have been determined.

Into an ice-cold solution of 160 g. of fuming nitric acid (sp. gr., 1.49–1.50), 40 g. of 1,3-dimethylbenzene was dropped. The reaction mixture was stirred during the addition (two hours). The reaction mixture was stirred for one-half hour more at room temperature and then heated at 120–130° for six hours under reflux. Upon pouring onto ice a solid product separated which was purified by recrystallization from 95 per cent. alcohol; m. p. 93°; yield, 35.5 g. (48%). Errera and Maltese report the same melting point, 93°.

4,6-Diamino-1,3-dimethylbenzene.—A solution of 9.8 g. of 4,6-dinitro-1,3-dimethylbenzene in 60 cc. of boiling absolute ethyl alcohol was reduced with 0.2 g. of platinum oxide catalyst and hydrogen. The diamine was purified by recrystallization from hot water; m. p. 104–105°;

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[4] Errera and Maltese, *Gazz. chim. ital.*, **33**, II, 277 (1903).

yield, 6.2 g. (92 per cent.). This product was previously prepared by E. Lehmann[5] by the reduction of the dinitro compound with zinc and hydrochloric acid. They reported a melting point of 103–104°.

4,6 - Di - (2,5 - dimethyl - 3 - carboethoxypyrryl) - 1,3-dimethylbenzene.—A mixture of 28 g. of 3-carboethoxy-2,5-hexadione and 10 g. of 4,6-diamino-1,3-dimethylbenzene in a 200-cc. flask fitted with a reflux condenser was heated for four hours at 110–120°. The water was then evaporated and a thick oil was obtained; yield, 29 g. (91%). The crude product was not purified but used directly for preparation of the acid.

4,6 - Di - (2,5 - dimethyl - 3 - carboxypyrryl) - 1,3-dimethylbenzene (III), (IV).—A mixture of 29 g. of the crude ester with 250 cc. of 10% alcoholic potassium hydroxide was heated for three hours on a steam-bath. Upon diluting the resulting solution to a volume of 1 liter with water and acidifying with dilute hydrochloric acid, a brownish precipitate was obtained. The product amounted to 19.7 g. (78%). For purification it was dissolved in 100 cc. of 10% aqueous sodium hydroxide and the dark-colored solution was extracted with hot chloroform from six to eight times to remove a considerable portion of the colored matter. It was then reacidified with dilute hydrochloric acid and the yellowish precipitate was filtered, dried and dissolved in 1200 cc. of *n*-butyl alcohol. The first fraction which crystallized out amounted to 4.3 g. This was recrystallized several times from *n*-butyl alcohol to a constant m. p. 305° (with dec.).

Higher-melting *trans* form (IV): m. p. 305°.

Anal. Calcd. for $C_{22}H_{24}O_4N_2$: N, 7.37; C, 69.47; H, 6.31. Found: N, 7.55; C, 69.62; H, 6.66.

The filtrate was evaporated to 400 cc. and 2.9 g. (m. p. 292–295°) of acid separated. On evaporation to 100 cc., 3.5 g. separated (m. p. 278–283°). These two fractions were discarded. The solution was then evaporated to 40 cc. and 6.2 g. of acid separated (m. p. 260–263°). This last portion was purified by recrystallization from ethyl alcohol, m. p. 260–262°.

Lower-melting *cis* form (III): m. p. 260–262°.

Anal. Calcd. for $C_{22}H_{24}O_4N_2$: N, 7.37; C, 69.47; H, 6.31. Found: N, 7.55; C, 69.61; H, 6.59.

Resolution of *trans*-4,6-Di-(2,5-dimethyl-3-carboxypyrryl)-1,3-dimethylbenzene.—A solution of 4.2 g. of brucine in 400 cc. of absolute methyl alcohol was heated to its boiling point and 4 g. of the powdered less soluble acid, m. p. 305°, was added slowly with stirring. After standing for several hours at 0°, the salt which separated was filtered. The first fraction thus obtained which amounted to 2.6 g. was recrystallized from absolute methyl alcohol to constant rotation, m. p. 186–190°.

Rotation. Less-soluble salt (*l*-brucine, *d*-acid): 0.1675 g. made up to 25 cc. with chloroform at 27° gave α_D +1.08; l = 2, $[\alpha]^{27}_D$ +80.63°.

Anal. Calcd. for $C_{45}H_{50}O_8N_4$: N, 7.23. Found: N, 7.23.

The filtrate from the less soluble salt was evaporated to about 150 cc. and again allowed to cool. The crystals separating were discarded. It was necessary to concentrate to dryness before the more soluble salt was obtained. It then separated from the methyl alcohol as a gum which, on long standing in a desiccator, solidified. It was found impossible to recrystallize this material, so the rotation was taken on the crude material, m. p. 152–159°.

Rotation. Crude more-soluble salt (*l*-brucine, *l*-acid). 0.1030 g. made up to 25 cc. with chloroform at 27° gave α_D −0.77; l = 2, $[\alpha]^{27}_D$ −93.44°.

***d* and *l* Acids.**—A suspension of 2 g. of either salt in 100 cc. of water was treated with 6 cc. of dilute hydrochloric acid and thoroughly stirred. The acid which precipitated was recrystallized from absolute ethyl alcohol to a constant m. p. of 275–276°.

Rotation. *d*-Acid. 0.09 g. made up to 25 cc. with pyridine at 27° gave α_D +1.24; l = 2, $[\alpha]^{27}_D$ +172.2.

Anal. Calcd. for $C_{22}H_{24}O_4N_2$: C, 69.47; H, 6.31. Found: C, 69.84; H, 6.68.

Rotation. *l*-Acid. 0.0792 g. made up to 25 cc. with pyridine at 27° gave α_D −1.05; l = 2, $[\alpha]^{27}_D$ −165.8.

Anal. Calcd. for $C_{22}H_{24}O_4N_2$: C, 69.47; H, 6.31. Found: C, 69.65; H, 6.50.

Racemization Experiments.—A solution of 0.1160 g. of *d*-acid in 50 cc. of 0.02272 *N* sodium hydroxide gave α_D +0.56; l = 2, $[\alpha]^{27}_D$ +120.68. Upon boiling for 107 hours the rotation gradually changed to $[\alpha]^{27}_D$ +53.9°.

No change in initial rotation was observed after boiling for three days in a pyridine solution.

Several alkaloidal salts were prepared but all fractions of any particular salt which separated from the solvent were proved to be identical. Only inactive acids identical with the original acid were obtained by decomposition of the various salts.

TABLE I

ALKALOIDAL SALTS OF *cis*-4,6-DI-(2,5-DIMETHYL-3-CARBOXYPYRRYL)-1,3-DIMETHYLBENZENE

		Rotation Made up to 25 cc. with pyridine: l = 2		
Mono salt[a]	M. p., °C.	Wt. salt	α_D	$[\alpha]^{27}_D$
Brucine	172–177	0.045	−0.17	−47.2
Strychnine	178–185	.2100	− .73	−43.5
Cinchonine	154–160	.1350	+ .86	+80.0

		N analyses, %	
Mono salt[a]	Formula	Calcd.	Found
Brucine	$C_{45}H_{50}O_8N_4$	7.23	7.52
Strychnine	$C_{43}H_{46}O_6N_4$	7.85	7.82
Cinchonine	$C_{41}H_{46}O_5N_4$	8.31	8.43

[a] Quinine and quinidine gave jelly-like salts in absolute methanol, ethanol and ethyl acetate.

1,4-Dimethyl-2-acetaminobenzene.—A solution of 50 g. of 1,4-dimethyl-2-aminobenzene in an equal weight of freshly distilled acetic anhydride was heated under reflux for twelve hours. Upon cooling, the reaction mixture solidified into a striped crystalline mass. It was purified by recrystallization from 35% alcohol; m. p. 138–139°; yield, 55.2 g. (82%). Schaumann[6] reported the same melting point.

1,4-Dimethyl-2-acetamino-5-nitrobenzene.—To a solution of 55 g. of 2-acetamino-1,4-dimethylbenzene in 50 cc. of concentrated sulfuric acid, 22 g. of concentrated nitric acid (sp. gr. 1.42) was added drop by drop. During the

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(5) Lehmann, *Ann.*, **163**, 350 (1872).

(6) Schaumann, *Ber.*, **11**, 1538 (1878).

addition, the reaction mixture was well cooled with ice and was mechanically stirred. After the addition, stirring was continued for two hours and then the reaction product was poured into 1 liter of water. The solid which separated was purified by crystallization from 95% alcohol; m. p. 167–169°; yield, 52 g. (74%).

This procedure is a modification of that used by Schaumann,[6] who reported a melting point of 192°. Nölting, Witt and Forel[7] reported a melting point of 166°.

1,4-Dimethyl-2-amino-5-nitrobenzene.—To a solution of 52 g. of 1,4-dimethyl-2-acetamino-5-nitrobenzene in 600 cc. of 95% alcohol, 30 cc. of concentrated sulfuric acid was added. The mixture was refluxed for three hours then the alcohol was distilled off and the product poured into about 500 cc. of water. Yellow leaflets separated which were purified by recrystallization from alcohol; m. p. 142°; yield, 26 g. (62%). This compound has been previously prepared by Nölting, Witt and Forel,[7] who report a melting point of 142°.

1,4-Dimethyl-2,5-diaminobenzene.—A solution of 16.6 g. (0.1 mole) of 1,4-dimethyl-2-amino-5-nitrobenzene in 80 cc. of boiling ethyl alcohol in the reaction bottle of a catalytic reduction apparatus was reduced with 0.2 g. of platinum oxide catalyst and hydrogen. The diamine was purified by recrystallization from benzene; m. p. 148–149°; yield, 12 g. (89%).

Nietzki[8] prepared this substance by reduction of 2-amino-5-azo-1,4-dimethylbenzene with zinc and hydrochloric acid. They reported a melting point of 150°.

2,5 - Di - (2,5 - dimethyl - 3 - carboethoxypyrryl) - 1,4-dimethylbenzene.—A similar procedure was used as with the previous dimethyldiaminobenzene. From 28 g. of 3-carboethoxy-2,5-hexadione and 10 g. of 1,4-dimethyl-2,5-diaminobenzene was obtained 28.5 g. of large rhombic crystals from the reaction mixture; m. p. 150–157°. This crude ester was fractionated to obtain *cis* and *trans* forms.

Separation of *Cis* and *Trans* Forms.—A solution of 28.5 g. of crude 2,5-di-(2,5-dimethyl-3-carboethoxypyrryl)-1,4-dimethylbenzene in 400 cc. of boiling 95% ethyl alcohol was filtered and upon cooling, 11.7 g. of ester (first fraction) separated. This was repeatedly recrystallized (8–10 times) to constant melting point 183–185°.

Anal. Calcd. for $C_{26}H_{32}N_2O_4$: N, 6.42. Found: N, 6.50.

The original filtrate from the first fraction was evaporated to 350 cc. and on cooling 6 g. of material was isolated; then to 200 cc. giving 3.6 g.; finally to 100 cc. giving 4 g. Only the last 4 g. was used. It was recrystallized from alcohol (8–10 times) to constant m. p., 158–160°.

Anal. Calcd. for $C_{26}H_{32}N_2O_4$: N, 6.42. Found: N, 6.58.

***Cis* and *Trans* Forms of 2,5-Di-(2,5-dimethyl-3-carboxypyrryl)-1,4-dimethylbenzene (V), (VI).**—Since the two stereoisomeric esters were difficult to separate from each other in pure condition by crystallization, the two stereoisomeric acids were separated.

***Trans* Form.**—A mixture of 8 g. of the partially purified ester which melted at 165–172° with 200 cc. of 10% alcoholic potassium hydroxide was heated for four hours on a steam-bath under reflux. The alcohol was distilled off and the white potassium salt was dissolved in 400 cc. of water. Upon acidifying with a little hydrochloric acid, a white precipitate separated. This acid was recrystallized several times from dioxane until a constant melting point of 455–460° (Maquenne block) was obtained; yield, 5.8 g. (84%).

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.47; H, 6.31. Found: C, 69.95; H, 6.40.

***Cis* Form.**—Ten grams of the partially purified ester, m. p. 152–157°, was hydrolyzed as described for the *trans* ester. The acid thus obtained was recrystallized several times from dioxane to constant m. p. of 419–422°.

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.47; H, 6.31. Found: C, 70.08; H, 6.32.

All attempts to prepare salts of the *cis* and *trans* forms resulted in failure. A wide variety of alkaloids and a wide variety of solvents were tested but in every instance the free acid separated rather than the salts, due, presumably, to the relative insolubility of the acids.

1,3 - Di - (2,5 - dimethyl - 3 - carboethoxypyrryl)-benzene.—When 10 g. of 1,3-diaminobenzene was added to 36 g. of 3-carboethoxy-2,5-hexadione in an atmosphere of nitrogen, heat was evolved and water separated out from the reaction mixture. After the heat evolution had ceased, the reaction mixture was heated for four hours at a temperature of 80–100°. The water was evaporated from the reaction mixture and an oily product obtained; yield, 33 g. (87%). The crude product was saponified without previous purification.

1,3 - Di - (2,5 - dimethyl - 3 - carboxypyrryl) - benzene.—A mixture of 33 g. of the crude ester and 300 cc. of 10% alcoholic potassium hydroxide was refluxed for five hours. The alcohol was distilled off and the salt was dissolved in 800 cc. of water and acidified with hydrochloric acid. A yellowish precipitate separated which amounted to 26 g. (92%). This product after drying was recrystallized several times from *n*-butyl alcohol until a constant m. p. 273–274° was obtained.

Anal. Calcd. for $C_{20}H_{20}O_4N_2$: C, 68.18; H, 5.68. Found: C, 68.43; H, 5.71.

All attempts to resolve with various alkaloids resulted in failure. All the salts were jelly-like in character.

Summary

1. *Cis* and *trans* diastereoisomeric forms of 4,6-di - (2,5 - dimethyl - 3 - carboxypyrryl) - 1,3-dimethylbenzene and of 2,5-di-(2,5-dimethyl-3-carboxypyrryl)-1,4-dimethylbenzene have been synthesized.

2. The *trans* modification of the former pair was resolved into its enantiomorphs, which were very stable to racemization.

3. 1,3-Di-(2,5-dimethyl-3-carboxypyrryl)-benzene was synthesized but could not be resolved.

URBANA, ILLINOIS

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[7] Nölting, Witt and Forel, *Ber.*, **18**, 2664 (1885).

[8] Nietzki, *ibid.*, **13**, 471 (1880).