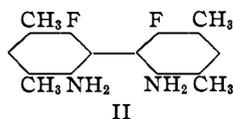
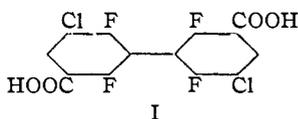


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Stereochemistry of Diphenyls. XXXI.¹ Preparation and Properties of 2,2',6,6'-Tetrafluoro- 3,3'-dicarboxy-5,5'-dichlorodiphenyl

BY E. C. KLEIDERER² AND ROGER ADAMS

In continuation of the investigation to determine the character of molecules containing atoms or groups of small volume in the 2,2',6,6' positions, the preparation of a tetrafluoro compound in this series has been undertaken. The specific substance finally obtained was 2,2',6,6'-tetrafluoro-3,3'-dicarboxy-5,5'-dichlorodiphenyl (I).



Under the conditions used it was found impossible to resolve this compound and no mutarotation of the salts was observed even at 0°. It would appear, then, that four fluorines are not sufficiently large to prevent free rotation of the phenyl groups.

A discussion of the structure of the 2,2'-difluoro-6,6'-diamino-3,3',5,5'-tetramethyldiphenyl (II) previously described by Kleiderer and Adams³ has appeared in "Annual Reports of the Chemical Society of London."⁴ Sidgwick has pointed out that if it is assumed that the hydrogen atoms of the amino groups in such a compound are turned out of the way, the inner spheres of the nitrogen and fluorine would not be expected to touch. He has presented a diagram drawn to scale illustrating this fact. He cites this as evidence that the repulsion of two groups extends beyond the range of the inner spheres and may be due to an envelope estimated at 0.5 Å. in thickness representing the large forces which cause the repelling of non-linked atoms.

Through the calculation previously made by Stanley and Adams⁵ the prediction was made that a diaminodifluorodiphenyl should be capable of resolution but easily racemized. These facts were borne out by experiment. In this calculation it was assumed that the hydrogens on the nitrogens did play a role in the interference of the two groups. It seems dubious whether it is proper to assume, as Sidgwick has done, that hydrogens or particularly other atoms and groups attached to the atom combined with the ring will not exert steric influence. If rotation of the nitrogen at-

(1) The previous paper in this series is, Searle and Adams, *THIS JOURNAL*, **55**, 1649 (1933). See 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) Kleiderer and Adams, *THIS JOURNAL*, **53**, 1575 (1931).

(4) Sidgwick, "Annual Reports Chem. Soc. of London," p. 69 (1932).

(5) Stanley and Adams, *THIS JOURNAL*, **52**, 1200 (1930).

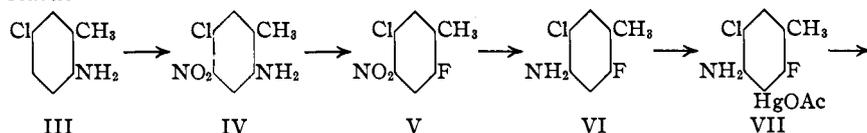
tached to the carbon of the ring occurs,⁶ the hydrogens on the nitrogen will be spinning in the circumference of a circle and should lead to a certain more or less constant, though perhaps small, residuum of interference extending beyond the inner sphere of the nitrogen atom. Moreover, the experimental evidence, though meager, is in favor of the assumption of an effect produced by atoms and groups on the atom attached to the ring. The restricted rotation in 2,5-di-(2,4-dimethylphenyl)-3,6-dibromohydroquinone⁷ was not existent in the corresponding quinone. In the quinone molecule there is no hydrogen on the oxygen as is found in the hydroquinone. It must be admitted, however, that other factors may be involved in those molecules since the quinone and the hydroquinone nuclei are decidedly different in character. It has been shown that $-\text{CONH}_2$ restricts rotation to a greater extent than a COOH group.⁸ An ethoxyl is more effective than a methoxyl in preventing free rotation of the rings.⁹

If a diagram is drawn for the tetrafluoro compound with the use of the same radii for fluorine and carbon as adopted by Sidgwick, it may be demonstrated that the two fluorines should not collide. Neither should they collide on the basis of calculations made by Stanley and Adams. On the other hand, if it is assumed that there is an envelope 0.5 Å. thick which may take part in the repulsion of the groups, resolution of the tetrafluoro compound might be expected. Since no resolution was obtained it may be concluded either that the effective envelope is much thinner than suggested by Sidgwick and that the inner spheres of two atoms must approach each other more closely in order to effect interference, or else that the hydrogens on a nitrogen or other atoms and groups attached to the atom combined to the ring contribute appreciably to the interference of 2,2' substituents.

The 2,2'-difluoro-6,6'-dimethoxy compound described by Becker and Adams¹⁰ was also non-resolvable but unfortunately as in the case of the hydrogens on the nitrogen there is no way to calculate the contribution of the methyl group to the interference of the methoxyl group. The conclusion that the methoxyl is less effective in interference than the amino group is warranted, since the corresponding amino derivative was resolvable.

Experimental

The preparation of the tetrafluoro compound (I) was made by the following series of reactions



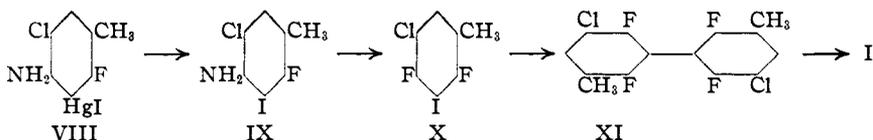
(6) Pauling, *Phys. Rev.*, **36**, 430 (1930); Hendricks, Posnjak and Kracek, *THIS JOURNAL*, **54**, 2766 (1932).

(7) Browning and Adams, *ibid.*, **52**, 4098 (1930).

(8) Stanley, McMahon and Adams, *ibid.*, **55**, 706 (1933).

(9) Li and Adams, unpublished results.

(10) Becker and Adams, *THIS JOURNAL*, **54**, 2973 (1932).



The structure of the 2-amino-3-methyl-5-chloro-6-nitrobenzene (IV) was determined by converting it through 3-methyl-5-chloro-6-nitrobenzene to 3-methyl-5-chloro-6-aminobenzene, the acetate of which had the properties of this compound as made through another series of reactions. In a similar manner the position of the acetoxy-mercuri group in 1-acetoxy-mercuri-2-fluoro-3-methyl-5-chloro-6-aminobenzene (VII) was determined by replacing the acetoxymercuri group with bromine and then comparing the product with the bromine compound made by another procedure which would lead with reasonable certainty to a molecule of that structure.

During the early stages of the investigation an attempt was made to oxidize 1-iodo-2,6-difluoro-3,5-dimethylbenzene to the corresponding monocarboxy compound from which it was intended to prepare the corresponding diphenyl. The product was always the dicarboxy compound, which was unsuitable for production of a diphenyl with the proper structure. It was also impossible to isolate a partial oxidation product of 2,2',6,6'-tetrafluoro-3,3',5,5'-tetramethyldiphenyl.

2-Amino-3-methyl-5-chloro-6-nitrobenzene (IV).—In a 600-cc. beaker 20 g. of 2-amino-3-methyl-5-chlorobenzene (III) was dissolved in 200 g. of concentrated sulfuric acid. The mixture was cooled to 0–5° and to this was added dropwise, with stirring, 13 g. of concentrated nitric acid (sp. gr., 1.42). After all of the nitric acid had been added, the mixture was stirred for thirty minutes longer and poured onto ice. This caused a precipitation of the amine and the amine sulfate, which was filtered off, made alkaline and the free base purified from 40% alcohol, from which it crystallized in orange needles melting at 123–124° (corr.). The yield was 24.5 g. (93%).

Anal. Calcd. for $\text{C}_7\text{H}_7\text{O}_2\text{N}_2\text{Cl}$: N, 15.01. Found: (micro Dumas) N, 15.25.

The acetate was prepared by warming a small amount of the amine with acetic anhydride. From water, it formed long white needles, melting at 140–141° (corr.).

Anal. Calcd. for $\text{C}_9\text{H}_9\text{O}_3\text{N}_2\text{Cl}_2$: N, 12.22. Found: (micro Dumas) N, 12.31.

According to Reverdin and Crépieux¹¹ the acetate of this amine melted at 262°. They prepared it as follows: 2,6-dinitro-3-methyl-5-chlorobenzene was obtained by nitration of *m*-chlorotoluene. This was reduced with alcoholic ammoniacal sulfur dioxide solution to 2-amino-3-methyl-5-chloro-6-nitrobenzene melting at 120°. They give, however, no proof for the structure of their amine.

In order to prove definitely the structure of the acetate melting at 140–141° (corr.) the following procedure was carried out: (IV) was diazotized in 95% alcohol and boiled to remove the amino group in the 2 position, forming 3-methyl-5-chloro-6-nitrobenzene. This compound was reduced with stannous chloride and hydrochloric acid to 3-methyl-5-chloro-6-aminobenzene, which was treated with acetic anhydride to form the acetyl derivative. This compound was prepared before by Cohen and Dakin¹² and Klotz.¹³ These authors reported its melting point as 113 and 114–115°, respectively. The melting point of the compound obtained above was found to be 114–115°.

3-Methyl-5-chloro-6-nitrobenzene-2-diazonium Borofluoride.—In a 300-cc. beaker was placed 25 cc. of concentrated hydrochloric acid containing a suspension of 15 g. of (IV). The mixture was cooled to 0° and a saturated solution of sodium nitrite was added slowly until all of the amine was in solution and until a slight excess of free

(11) Reverdin and Crépieux, *Ber.*, **33**, 2507 (1900).

(12) Cohen and Dakin, *J. Chem. Soc.*, **81**, 1337 (1902).

(13) Klotz, *Ann.*, **231**, 311 (1885).

nitrous acid was present (starch iodide test). The solution was filtered from sodium chloride and to the filtrate was added 28 g. of a solution of hydroborofluoric acid, made by mixing 20 g. of 48% hydrofluoric and 8 g. of boric acid. Upon addition of the acid, the borofluoride slowly crystallized out. The solution was allowed to stand for two hours at 0° and filtered. No purification was attempted. The yield was 14 g. (61%); dec. pt. 153° (corr.).

Anal. Calcd. for $C_7H_6O_2N_2Cl \cdot BF_4$: N, 14.70. Found: (micro Dumas) N, 15.64.

2-Fluoro-3-methyl-5-chloro-6-nitrobenzene (V).—The borofluoride just described was heated in small amounts (4–5 g.) *in vacuo* to 170°. The crude fluoride was distilled with steam from alkaline solution. The yield from 70 g. of borofluoride was 23 g. of fluoride (49.5%); b. p. 247° (750 mm.); m. p. 18–19°; n_D^{25} 1.5416; d_{25}^{25} 1.411.

Anal. Calcd. for $C_7H_6ClFN_2O_2$: N, 7.39. Found: (micro Dumas) N, 7.59.

2-Fluoro-3-methyl-5-chloro-6-aminobenzene (VI).—Five grams of V was reduced with stannous chloride³ in a mixture of glacial acetic acid and concentrated hydrochloric acid. After complete reduction the solution was made alkaline with sodium hydroxide and the amine distilled from the reaction mixture. It formed shining white plates, which melted after crystallization from 50% alcohol at 55–56° (corr.); yield, quantitative.

Anal. Calcd. for C_7H_7NCIF : N, 8.75. Found: (micro Dumas) N, 8.81.

The acetate formed by treatment of the base with acetic anhydride was crystallized from water, m. p. 138–139° (corr.).

Anal. Calcd. for C_9H_9ONClF : N, 6.96. Found: (micro Dumas) N, 7.14.

1-Acetoxy-mercuri-2-fluoro-3-methyl-5-chloro-6-aminobenzene (VII).—To a solution of 50 g. of VI in 250 cc. of absolute methyl alcohol was added 100 g. of mercuric acetate dissolved in 300 cc. of absolute methyl alcohol. After four hours the mixture was diluted with 700 cc. of water and allowed to stand overnight when VII separated out of solution in cotton-like needles. Purified from acetic acid it had a m. p. 216–218° (corr.) with dec.

Anal. Calcd. for $C_7H_6ClFN(HgOCOCH_3)$: Hg, 48.08. Found: (pptd. as HgS) Hg, 48.3.

1-Iodo-mercuri-2-fluoro-3-methyl-5-chloro-6-aminobenzene (VIII).—To a suspension of VII was added 116 g. of potassium iodide dissolved in 200 cc. of water and the mixture was warmed for thirty minutes on the steam-bath, which caused the formation of VIII. No means of purification was found; m. p. 275–279° (corr.), with dec. The crude product was used directly for the next step.

Anal. Calcd. for $C_7H_6ClFN(HgI)$: Hg, 41.35. Found: (pptd. as HgS) Hg, 41.65.

1-Iodo-2-fluoro-3-methyl-5-chloro-6-aminobenzene (IX).—To a suspension of VIII was added 500 cc. of methyl alcohol and 77 g. of iodine dissolved in 400 cc. of methyl alcohol. After adding the iodine the iodo derivative remained in solution and the mercuric iodide also as K_2HgI_4 . The volume of the solution was reduced to one-half by evaporation and diluted with water, causing IX to separate in fine yellow needles. After purification from 60% methyl alcohol, m. p. 67–68° (corr.); yield, 78.5 g. (88% calcd. on VI).

Anal. Calcd. for C_7H_6NCIF : N, 4.90. Found: (micro Dumas) N, 4.99.

The acetate prepared by dissolving the amine in acetic anhydride and adding several drops of concentrated sulfuric acid was purified by crystallization from 50% ethyl alcohol; m. p. 203–204° (corr.).

Anal. Calcd. for $C_9H_8NOIFCl$: N, 4.28. Found: (micro Dumas) N, 4.38.

In order to prove that the acetoxy-mercuri group was substituted in the 1 position, the following experiments were followed out. In glacial acetic acid, VI was brominated, using bromine dissolved in glacial acetic acid, yielding 1-bromo-2-fluoro-3-methyl-5-chloro-6-aminobenzene; m. p. 61–62° (corr.). A portion of VII was treated with an excess of aqueous sodium bromide solution forming 1-bromo-mercuri-2-fluoro-3-methyl-5-chloro-6-aminobenzene. This compound was treated with bromine in chloroform which caused the bromo-mercuri residue to be replaced by bromine. The compound obtained in this way melted at 61–62° (corr.), and a mixed melting point of the two showed no depression. Since these two compounds were identical, the acetoxy-mercuri group was in position 1 and hence the iodine of VIII is very probably in position 1.

1-Iodo-2-fluoro-3-methyl-5-chlorobenzene-6-diazonium-borofluoride.—This compound was prepared in a manner similar to the previously described borofluoride using IX as starting material. From 20 g. of the amine 18 g. of the borofluoride was obtained (65%), dec. pt. 218° (corr.).

Anal. Calcd. for $C_7H_4BClF_2IN_2$: N, 7.68. Found: (micro Dumas) N, 8.09.

1-Iodo-2,6-difluoro-3-methyl-5-chlorobenzene (X).—The decomposition of the borofluoride was carried out as described for other borofluorides. The temperature of decomposition was 220°. X was purified by distillation, b. p. 244–246° (corr.). From 20 g. of the borofluoride, 13 g. of the fluoride was obtained (85%). This was converted directly into the diphenyl.

2,2',6,6'-Tetrafluoro-3,3'-dimethyl-5,5'-dichlorodiphenyl (XI).—A mixture of 1 g. of X and 1 g. of activated copper was treated for two hours at 200°. The mixture was extracted with acetone, treated with norite and filtered. Water was added to help precipitate the crude diphenyl, which was crystallized from alcohol; m. p. 137–138° (corr.); yield, 0.3 g. (34%).

Anal. Calcd. for $C_{14}H_8Cl_2F_4$: Cl, 21.90. Found: (micro) Cl, 22.16.

2,2',6,6'-Tetrafluoro-3,3'-dicarboxy-5,5'-dichlorodiphenyl (I).—A mixture of 0.5 g. of XI and 4 cc. of concentrated nitric acid diluted with 14 cc. of water was heated at 160° for twenty hours in a sealed tube. The acid was dissolved in sodium hydroxide solution and filtered from any unreacted diphenyl. The acid was reprecipitated with dilute sulfuric acid and crystallized from 50% alcohol; fine needles, m. p. 295–298° (corr.) with shrinking at 285°. The yield was 0.5 g. (84.5%).

Anal. Calcd. for $C_{14}H_4O_4Cl_2F_4$: Cl, 18.44; n. e., 172.5. Found: (micro) Cl, 18.54; n. e., 171.9.

ATTEMPTED RESOLUTION OF I

Salt	Wt. to 10 cc. in alcohol, g.	$l = 1$ α_D	$[\alpha]_D^{20}$	Formula	Nitrogen, % Calcd. Found
Cinchonidine	0.1000	-0.65°	-65°	$C_{14}H_4O_4F_4Cl_2 \cdot C_{19}H_{22}ON_2$	4.37 4.60
Strychnine	.1500	-.64	-42.7	$C_{14}H_4O_4F_4Cl_2 \cdot (C_{21}H_{22}N_2O_2)_2$	5.33 5.39
Morphine	.1500	-1.35	-90	$C_{14}H_4O_4F_4Cl_2 \cdot (C_{17}H_{19}NO_3)_2$	2.93 3.05

The salts were prepared in alcohol. The cinchonidine salt was precipitated fractionally from alcohol by addition of ether. The strychnine salt was fractionated from chloroform; the morphine salt from acetone. All fractions of each salt gave the same rotation, no mutarotation and on decomposition gave inactive acids.

1-Acetoxy-mercuri-2-fluoro-3,5-dimethyl-6-aminobenzene.—To a solution of 50 g. of 2-fluoro-3,5-dimethyl-6-aminobenzene¹⁰ in 250 cc. of absolute methyl alcohol was added 100 g. of mercuric acetate dissolved in 300 cc. of absolute methyl alcohol. The mixture was allowed to stand four hours and then diluted with 700 cc. of water and allowed to stand overnight in a cool place when 1-acetoxy-mercuri-2-fluoro-3,5-dimethyl-

6-aminobenzene separated out of solution in fine needles. Purified from acetic acid it had a melting point of 207–208° (corr.) with dec.

Anal. Calcd. for $C_6H_5FN(HgOCOCH_3)$: Hg, 50.6. Found: (pptd. as HgS) Hg, 50.9.

1-Iodo-mercuri-2-fluoro-3,5-dimethyl-6-aminobenzene.—A suspension of 50 g. of the 1-acetoxy-mercuri compound in water was treated with 58 g. of potassium iodide. The mixture was heated, causing the precipitation of the insoluble mercuric iodide derivative which melted with decomposition at 235–240° (corr.). The yield was quantitative.

Anal. Calcd. for $C_8H_8FN(HgI)$: Hg, 43.13. Found: (pptd. as HgS) Hg, 43.50.

1-Iodo-2-fluoro-3,5-dimethyl-6-aminobenzene.—To the aqueous methyl alcoholic suspension of 1-iodo-mercuri-2-fluoro-3,5-dimethyl-6-aminobenzene from the above preparation was added 80 g. of iodine dissolved in 400 cc. of methyl alcohol. After cooling, the mercuric iodide precipitated out and the product remained in solution. After filtration the methyl alcohol was distilled off and the compound crystallized from 50% alcohol, m. p. 53–54°.

Anal. Calcd. for C_8H_8FIN : I, 47.92. Found: (micro Dumas) I, 48.15.

In order to prove that the acetoxy-mercuri group had substituted in position 1, the compound obtained by bromination of 2-fluoro-3,5-dimethyl-6-aminobenzene in glacial acetic acid was compared with the compound obtained by treating 1-acetoxy-mercuri-2-fluoro-3,5-dimethyl-6-aminobenzene with aqueous sodium bromide and then with bromine in chloroform. Both of these compounds melted at 56° (corr.) and the mixed melting point showed no depression. This compound, 1-bromo-2-fluoro-3,5-dimethyl-6-aminobenzene, had been previously described by Becker and Adams.¹⁰

1-Iodo-2-fluoro-3,5-dimethylbenzene-6-diazonium Borofluoride.—As described previously for analogous compounds, 1-iodo-2-fluoro-3,5-dimethyl-6-aminobenzene was converted to the borofluoride. From 20 g. of the amine 17 g. of the borofluoride was obtained (65%); dec. pt. 235° (corr.).

1-Iodo-2,6-difluoro-3,5-dimethylbenzene.—The decomposition of the borofluoride was carried out in a 500-cc. distillation flask heated to 200° to which was connected a reflux condenser. From 10 g. of borofluoride 5.5 g. of fluoride was obtained (75%). The fluoride was purified by steam distillation and by crystallization from low-boiling petroleum ether; m. p. 42–43° (corr.).

Anal. Calcd. for $C_8H_7F_2I$: I, 47.5. Found: (micro Dumas) I, 47.8.

1-Iodo-2,6-difluoro-3,5-dicarboxybenzene.—A mixture of 2 g. of 1-iodo-2,6-difluoro-3,5-dimethylbenzene and 10 cc. of nitric acid (sp. gr., 1.42) diluted with 20 cc. of water was heated in a sealed tube for thirty-six hours at 160°. The purpose of the preparation was to produce 1-iodo-2,6-difluoro-3-methyl-5-carboxybenzene, but in no case could any monocarboxylic acid be isolated. The dicarboxylic acid was crystallized from water. The yield was 2 g. (85%); m. p. 223–226°.

Anal. Calcd. for $C_8H_3O_4F_2I$: I, 38.7. Found: (micro Dumas) I, 39.2.

2,2'-6,6'-Tetrafluoro-3,3',5,5'-tetramethyldiphenyl.—A mixture of 2 g. of 1-iodo-2,6-difluoro-3,5-dimethylbenzene and 2 g. of active copper was heated for two hours at 200°. The mixture was extracted with acetone and filtered. Water was added to precipitate the crude diphenyl, which was crystallized from 70% alcohol. The yield was 0.63 g. (60%); m. p. 149–150° (corr.). The analysis of this compound is interesting since it was the only case in this investigation in which the carbon and hydrogen determinations of a fluorinated compound gave satisfactory results.

Anal. Calcd. for $C_{16}H_{14}F_4$: C, 68.15; H, 4.97. Found: (micro) C, 68.36; H, 4.90.

Copper Bronze.—Ordinary copper bronze sometimes gave very satisfactory and sometimes very poor results in the Ullmann condensation. A simple treatment of the commercial copper bronze made possible more uniform results and frequently made possible a more rapid reaction at a lower temperature.

The copper bronze was treated with a 2% solution of iodine in acetone for about five to ten minutes. This caused it to turn rather grayish in color due to the formation of copper iodide. The product was filtered and treated with dilute hydrochloric acid in acetone. The copper iodide dissolved and the copper bronze remaining was filtered and washed with acetone. It was then dried in a vacuum desiccator. It was found preferable to use this bronze immediately after preparation.

Analysis of Organic Mercury Compounds.—Analyses for mercury were made by a combination of two methods. For the decomposition of the organic mercury compound the method of Tabern¹⁴ was used. The determination of the soluble mercury compound was made through hydrogen sulfide precipitation and weighing of the mercuric sulfide.

Summary

1. 2,2',6,6'-Tetrafluoro-3,3'-dicarboxy-5,5'-dichlorodiphenyl has been prepared. It could not be resolved. The structure of this molecule and of others of a similar character has been discussed.

(14) Tabern and Shelberg, *Ind. Eng. Chem., Anal. Ed.*, **4**, 401 (1932).

URBANA, ILLINOIS

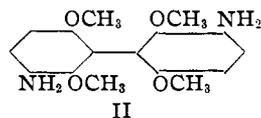
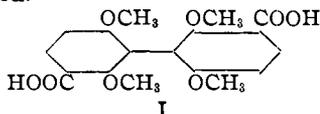
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Stereochemistry of Diphenyls. XXXII.¹ Preparation and Properties of Certain 2,2',6,6'-Tetramethoxydiphenyls

By A. M. VANARENDONK,² M. E. CUPERY AND ROGER ADAMS

Simultaneously with the preparation and study of the 2,2',6,6'-tetrafluorodiphenyl described in the previous paper in this series, the synthesis of 2,2',6,6'-tetramethoxydiphenyls has been undertaken. Two compounds 2,2',6,6'-tetramethoxy-3,3'-dicarboxydiphenyl (I) and 2,2',6,6'-tetramethoxy-3,3'-diaminodiphenyl (II) have been produced and the properties determined.



The dicarboxy compound could not be resolved. No mutarotating salts could be obtained even at -17° and no active acid by decomposition of any of the salts.

Resolution of the diamino compound was attempted through the di-

(1) For the previous paper in this series see Kleiderer and Adams, *THIS JOURNAL*, **55**, 4219 (1933); see 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.