

THE SYNTHESIS OF CERTAIN SUBSTITUTED
sym-DIPHENYLCARBAZIDES.

A thesis submitted to the Chemistry
Department of Washington and Lee
University as a partial fulfillment
of the requirements for the degree
of Bachelor of Science in Chemistry.

August 21, 1943

Frederick William Bauer

Under the direction of Professor J.R. Taylor

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SCIENTIFIC RESEARCHES

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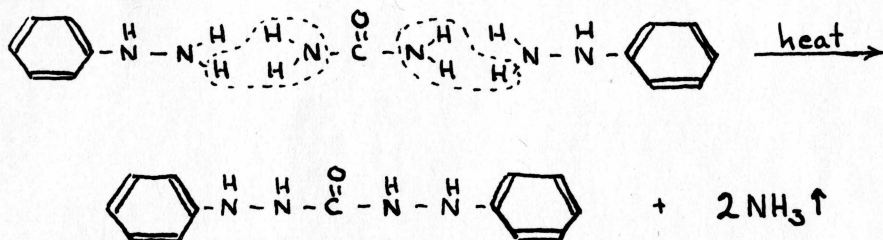
I wish at this time to acknowledge certain preliminary work performed and suggestions made by Professor Taylor which greatly advanced and aided the work of the author.

F.W.B.

I. Introduction.

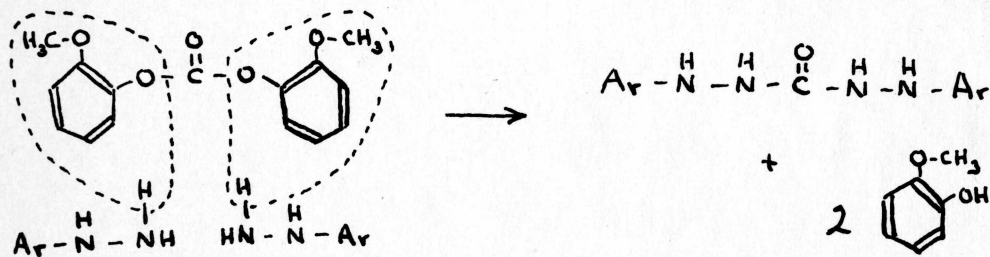
In the spring of 1943 James S. Parsons¹ in working on his B.S. Thesis, found that the compound, diphenylcarbazine, could be used to determine cadmium ion quantitatively by a colorimetric analysis. However, the reagent is insoluble in water and therefore must be used in acetone or some other non-polar solvent. Since the acetone solution evaporated so readily, changing the concentration, it was the aim of this research to try to synthesize similar compounds with various groups substituted on the phenyl radicals which would lead to water solubility. It was proposed to make the substitution of the carboxyl, sulfonyl, and hydroxyl groups in various positions and test their solubility and then, if possible, try them as reagents in a quantitative test. The latter stage was, however, never reached.

The general method of preparation was to diazotize the substituted aniline and then to reduce the diazonium compound to the corresponding phenylhydrazine. The phenylhydrazine could then be coupled with a carbonyl group by heating two moles of the hydrazine with one mole of urea until ammonia ceased to be evolved. This reaction occurs in the following way:



The resulting mass could be recrystallized from hot water and might be useful for analysis. At this point, great difficulty arose: the high water solubility of these compounds made them hard to recrystallize.

The ordinary method for coupling was to heat the 2 : 1 - molar mixture in a beaker set in an oil bath at a temperature slightly higher than the melting point of urea, until all of the ammonia had evolved. This was the method used throughout the experimental work of this thesis. There were, however, two alternate methods recorded in the literature. [I] The method whereby similar molar concentrations were heated in amyl alcohol until ammonia stopped coming off.² [II] The reaction of the hydrazine with guaiacol carbonate, which proceeds as follows:³



In the preparation of the hydrazines, several different reducing agents were tried, namely: zinc dust and acetic acid; sodium hydrosulfite; and stannous chloride and hydrochloric acid. These were suggested by various authors in their preparations of certain substituted hydrazines and were used according to the authors' preference in the original syntheses.

The following is a detailed account of the experimental procedures of the various syntheses undertaken.

II. Preparation of p,p'-dicarboxy-diphenyl-carbazide.

The first step in this synthesis was the preparation of the hydrochloride of p-carboxyphenylhydrazine according to the French⁴ method. 27.4 gm. of p-aminobenzoic acid [anthranilic acid] were dissolved in 500 cc. water and 40 cc. HCl [d=1.19]. The solution was cooled to 0° C and mechanically agitated while a previously cooled solution of 15 gm. of sodium nitrite in 50 cc. of water was added dropwise; the solution was carefully kept under 5° C. At the end of the addition, a solution of 125 gm. of sodium sulfite heptahydrate in 400 cc. of water was added. The solution was red, changing to yellow on standing for about an hour. To this yellow solution was added 15 cc. of glacial acetic acid and a pinch of zinc, which was intended to complete reduction of the diazo compound to the hydrazine. The solution was then heated on a steam bath for one hour; the color remained pale yellow.

750 cc. of HCl [d=1.19] was added to this solution and after boiling off part of the excess water and cooling, white crystals precipitated. These were recrystallized by dissolving in 15 parts of water and adding 5 parts of concentrated HCl to reprecipitate the hydrochloride. After drying, the compound decomposed at 195° C.; the compound prepared by Stig Veibel and Niels Hauge decomposed at 240° C. To verify the composition of the substance as the hydrochloride of p-hydroxyphenylhydrazine, a Volhard⁵ chloride determination was carried out.

1.5278 gm. of the compound were dissolved in water and made up to 100 ml. ; one-fifth aliquot portions were titrated with 0.088 N AgNO₃; 22.71 ml. were used. Calculations will be found on next page.

$$[22.71] [0.088] = 1.998 \text{ me. Cl}^-$$

$$\frac{[1.998] [0.03546] [5]}{1.5278} = 18.56 \% \text{ Cl}$$

$$\text{Calculated} = 18.83 \% \text{ Cl}$$

Since the compound had strong reducing properties as shown by Tollens' test⁶, which is a characteristic of the phenylhydrazines, and the Cl determination was so close to the calculated value, it was assumed that the compound prepared was the hydrochloride of p-carboxyphenylhydrazine.

Because the hydrazonium ions would decompose the urea used in the coupling of the two hydrazines to the carbonyl group, the hydrochloride had to be converted into the sodium salt of the carboxylic acid. This was accomplished as follows: the hydrochloride was dissolved by warming to 75° C. in the least amount of 6 N NaOH, and was then reprecipitated by adding 30% NaOH. Brownish crystals were formed and were filtered off through sintered glass by suction and then dried. Since the filtrate was strongly basic it was assumed that the conversion was satisfactory.

19.5 gm. [0.11 mole] of the sodium salt were mixed thoroughly with 3 gm. [0.055 mole] of urea in a beaker and placed in an oil bath. The temperature was slowly raised to about 120° C. when the mixture softened, and small amounts of ammonia were plainly detected by moist litmus paper and odor. The brownish mass softened to a paste and then dried out completely. To this mass water was added slowly until all dissolved. The solution was stirred vigorously as more ammonia was evolved; when evolution of ammonia ceased, the solution was allowed to cool and a brown mass crystallized out.

This mass was filtered and recrystallized from boiling water by adding water dropwise through a Liebig condenser attached to a flask in an oil bath kept at 100° C. This was necessary since the crystals are extremely soluble in water and very difficult to get out in the pure form. Upon each recrystallization the crystals become lighter and lighter colored, but the yield decreases very rapidly due to the great solubility. For this reason, only two recrystallizations were carried out.

In an effort to verify the formation of the diphenylcarbazine, a Kjeldahl nitrogen determination⁷ was undertaken. 0.2660 gm. of the substance were weighed on a quantitative filter paper and put into a Kjeldahl flask with 10 gm. of K₂SO₄, 0.3 gm. CuSO₄, and 35 ml. of concentrated H₂SO₄. The contents were digested over night and then excess base was added and the ammonia distilled over into 49.43 ml. of 0.1570 N HCl and back titrated with 37.71 ml. of 0.1490 N NaOH :

$$[49.43] [0.1570] = 7.76 \text{ me.}$$

$$[37.71] [0.1490] = 5.62 \text{ me.}$$

$$\underline{\hspace{10em}} \\ 2.14 \text{ me. NH}_3 \equiv \text{N}$$

$$[2.14] [0.014] = 0.0299 \text{ gm. N}$$

$$\frac{0.0299 \times 100}{0.2660} = 11.25 \% \text{ N}$$

$$\text{Calculated} = 16.95 \% \text{ N}$$

This low value probably arises from the fact that the sample analyzed was impure and also in that an ordinary Kjeldahl determination is not always satisfactory since the hydrazine group is easily oxidized and some nitrogen may be lost as the oxides or as nitrate.

Parsons¹ found analogous low results in his hydrazine analysis. No further investigation was carried out on this compound. However, with a method for obtaining the pure carbazide by recrystallization, the synthesis may be practicable in this way.

III. p,p'-disulfonicdiphenylcarbazide.

This preparation begins with the synthesis of phenylhydrazine-p-sulfonic acid as described by Thompson⁸. 19 gm. of sulfanilic acid dissolved in 23 ml. of 20% NaOH and 100 ml. of H₂O were cooled to 0° C. and diazotized with 7 gm. NaNO₂ in 50 ml. of H₂O, previously cooled. This diazo compound was poured into a cold mixture of 12 ml. of conc. H₂SO₄ in 100 ml. of H₂O. The resulting compound was filtered off, stirred to a paste with water and reduced with a cold solution of 22 gm. of sodium hydrosulfite [Na₂S₂O₄.2H₂O] in 125 ml. of H₂O with 20 ml. HCl being added during the reduction. When the reduction was complete, 30 ml. of conc. HCl were added and the solution was boiled down to crystallization; this gives the free base.

Cummings⁹ proposed another method for its preparation using NaHSO₃ as a reducing agent. This procedure was carried out by Dr. Taylor and gave satisfactory results also.

The compound obtained by the author was analyzed by a crude equivalent weight determination in which 0.5644 gm. of the compound was dissolved in water and titrated with standard base, using phenolphthalein as indicator. 18.97 ml. of 0.15 N base were required.

$$[18.97] [0.15] = 2.83 \text{ me.}$$

$$\frac{0.5644 \text{ gm.}}{2.83 \text{ me.}} = 0.199 \text{ gm./me} = 199 \text{ gm./eq.}$$

Calculated = 188 gm/eq.

This value was considered sufficiently close to distinguish the compound from other possible substances since the hydrazine group has some influence on the total base required.

Before attempting the synthesis of the carbazide, the hydrazine was converted into the sodium salt by dissolving in the least amount of 2 N NaOH using a reflux condenser similar to the arrangement used in recrystallizing the p-carboxyphenylhydrazine. Recrystallization was extremely successful with the crystals large and well formed on cooling.

A modification of the coupling procedure was tried with the sodium salt, in that 0.36 gm. [0.006 mole] of urea were first melted; then 2.55 gm. [0.012 mole] of the salt was added a little at a time. This seemed satisfactory, but even so, no actual liquefaction took place. However, the resulting mass was in a much purer state since it was not nearly as dark as the mass obtained from the carboxy derivative. After similar recrystallization using the oil bath and reflux condenser, a fairly pure substance was formed which could not be melted in the highest obtainable temperature in a dibutylphthalate bath.

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A modified Kjeldahl in which calcium oxalate is used to prevent the oxidation of the hydrazine to free nitrogen was used. 0.2844 gm. of substance was digested with 35 ml. of concentrated H_2SO_4 and CaC_2O_4 . It was made basic and the ammonia distilled into 49.81 ml. of 0.1570 N HCl, and back titrated with 32.65 ml. of 0.1490 N NaOH.

$$[0.1570] [49.81] = 7.82 \text{ me.}$$

$$[0.1490] [32.65] = \underline{4.87 \text{ me.}}$$

$$2.95 \text{ me. } NH_3 \equiv N$$

[Calculation concluded on the following page.]

$$[2.95] [0.014] = 0.0413$$

$$\frac{0.0413 \times 100}{0.2844} = 14.5 \% \text{ N}$$

Calculated = 12.5 % N

This is definitely much nearer the calculated value than was the case in the carboxyl derivative, which is probably because of the higher degree of purity and the modified method of analysis. Even so, it is still desirable to acquire some knack in the recrystallization of these highly soluble substances so that they can be obtained in the pure form.

IV. *p,p'*-dihydroxydiphenylcarbazide.

Only one reference to the *p*-hydroxyphenylhydrazine could be found in the literature. This was a note in the Chemical Abstracts¹¹ which gave a Japanese method of an electrolysis of *m*-xylylene, yielding 50 % 4-hydroxyphenylhydrazine and 50 % 2,4-dimethylphenylhydrazine. This method was discarded, however, since organic electrolyses heretofore have not given very satisfactory results, and the starting compound was not available in this laboratory.

Therefore a modification of Cumming's⁹ preparation of the sulfonic derivative was undertaken. 29.1 gm. of *p*-aminophenol were dissolved in 200 ml. of water and 18 gm. concentrated H₂SO₄. This solution was diazotized by adding dropwise over a period of one-half hour 21 gm. of NaNO₂ in 50 ml. of water until a reaction was obtained with potassium iodide-starch paper. The temperature was maintained below 5° C. This solution was added to 130 gm. of Na₂SO₃ in 400 ml. of water at 5° C° and allowed to stand 15 minutes in an ice bath. It was then allowed to warm in the air one hour and was then digested

on a steam bath while being made strongly acid with concentrated HCl. An intensely red solution resulted with a very characteristic phenolic odor. Zinc dust was added in an effort to decolorize the solution, but instead, a tar began to appear. This was filtered off and the red solution was boiled down until crystals in the shape of pyramids began to crystallize out. The solution was then cooled and these white crystals filtered off and dried. When heated on a crucible lid they exploded like pop corn but did not burn; so they were therefore considered to be an inorganic salt and discarded. The filtrate, still red, was treated with decolorizing carbon and again filtered. The red color remained. A small portion was then extracted with three equal portions of benzene made slightly acidic with acetic acid to release free hydroxyl or hydrazine, if present. The benzene was then evaporated off over a water bath, but nothing could be obtained.

The remainder of the solution was made basic with NaOH in large excess. A faint precipitate appeared, similar to the ferric and aluminum hydroxides, which was assumed to be zinc hydroxide from the zinc used to decolorize the solution. It was noted that when the solution was basic, it possessed a blue color to reflected light and a red color in transmitted light - reason unknown - except that the aromatic ring compounds highly substituted are apt to act accordingly, for example, fluorescein. When the basic solution was boiled down again, the same white crystals came out. At this point, further investigation seemed useless and the solution was laid aside.

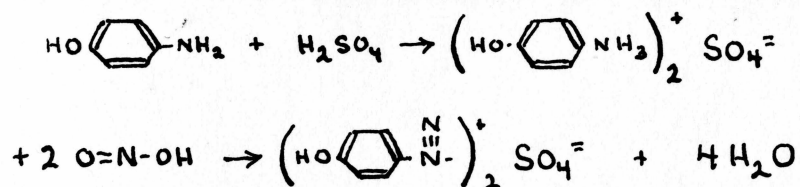
It is probably because most of the phenols so easily polymerize and form tars that nothing could be recovered by this method. Also when a phenolic group is present the temperature is best kept at -20° C. or below for the most satisfactory results. Since these requirements

could not be met in the scope of this laboratory the effort to procure the hydroxy derivative of the diphenylcarbazide was abandoned.

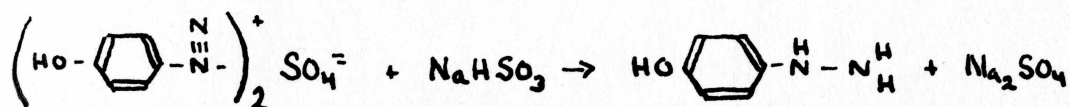
The meta or ortho derivatives were not given much attention in the literature, except for the o-carboxyphenylhydrazine. A last effort was concerned with this compound but the method of preparing it according to Fischer¹² did not turn out as expected. The precipitation of the hydrochlorides of o-carboxyphenylhydrazine and anthranilic acid along with NaCl was satisfactory, but when an attempt to separate them was made, nothing could be recovered. At this stage, the experimental work was brought to a close.

Summary.

It is perhaps advisable here to give a complete resume of the reactions involved in these syntheses. In all cases, a substituted aniline was the starting product which was diazotized with NaNO_2 in acid solution at a temperature maintained between 0° and 5° C.



The diazo compound was then reduced, either with $\text{Na}_2\text{S}_2\text{O}_4$, Zn and HAC, Na_2SO_3 , or SnCl_2 [not used in the experiments carried out in this thesis].



The products obtained are extremely impure and very water soluble; thus their further purification is the major problem to overcome. Little success is obtained in the general method for recrystallization; therefore the method using the reflux condenser was applied with moderate success. Yields are not high to begin with, and decrease rapidly on several recrystallizations.

As for actual formation of the substituted diphenylcarbazides, those bearing the sulfonyl group seemed the easiest to make and the hydroxy derivatives by far the most difficult.

In closing, it may be said that the possibility of preparing the substituted diphenylcarbazides is good, and with the proper amount of care and patience, it should not be too difficult to get several. These could be used further to investigate the cadmium ion, in water solution, and perhaps solve some of the difficulties that arise from

such interfering cations as zinc and so forth. Time and patience are the only real drawback in their ultimate synthesis.

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