[CONTRIBUTION FROM THE KETTERING LABORATORY OF APPLIED PHYSIOLOGY, COLLEGE OF MEDICINE, UNIVERSITY OF CINCINNATI]

Synthesis of Di-beta-naphthylthiocarbazone and Some of its Analogs*

BY DONALD M. HUBBARD AND EUGENE W. SCOTT

Since Suprunovich[1] first called attention to the usefulness of di-β-naphthylthiocarbazone as an analytical reagent for the detection and estimation of certain metals, this new reagent has been successfully employed in the determination of mercury[2] and zinc[3] in biological materials. The compound is not commercially available and therefore has now been synthesized in this laboratory. Two methods were tried—that described by Suprunovich,[1] a method similar to Fischer's procedure for the synthesis of dithizone,[4] and another analogous to that described by Bamberger[5] who also synthesized dithizone. Suprunovich's method did not prove successful in our hands, but a very small amount of di-β-naphthylthiocarbazone was obtained by slightly modifying his procedure. This modified method has been given in a recent paper on the determination of mercury.[2] Bamberger's method[5,6] was first tried for synthesizing dithizone and then was adapted successfully to the synthesis of di-β-naphthylthiocarbazone and a few other analogs of dithizone. The synthesis was accomplished in three steps—(a) the coupling of diazotized β-naphthylamine with nitromethane to produce the nitroformazyl, (b) the formation of di-β-naphthylthiocarbazide by the reduction of the nitroformazyl compound with ammonium sulfide, and (c) the formation of the carbazone by partial oxidation of the carbazide.

Experimental

Formation of the Nitroformazyl Compound

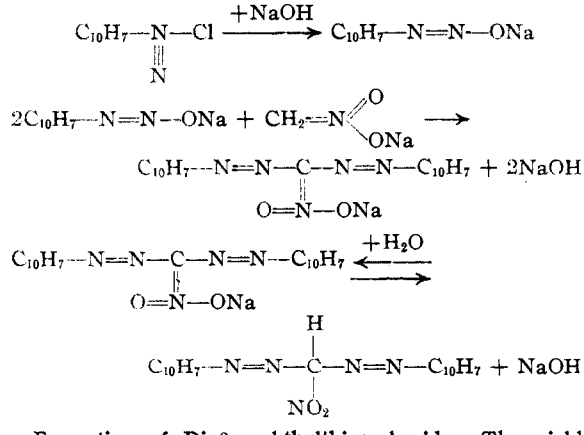
Sodium Hydroxide Solution.—An aqueous solution of sodium hydroxide is prepared by dissolving 25 g. of sodium hydroxide in water and adjusting the volume to 100 ml.

Sodium Acetate Solution.—This solution is prepared by dissolving 40 g. of $NaOAc \cdot 3H_2O$ in sufficient water to make 100 ml. of solution.

Alkaline Nitromethane Solution.—This solution is prepared by mixing 4.8 ml. of the sodium hydroxide solution with 13.5 ml. of absolute alcohol and 1.6 ml. (0.03 mole) of nitromethane. The mixture is cooled to −5° with crystal formation, and 100 ml. of cold water added, the mixture being shaken until the crystals are in solution, when it is again cooled to −5°. Just before use, the solution is mixed with another 4.8-ml. portion of the sodium hydroxide solution and is placed in a separatory funnel containing a little cracked ice.

β-Naphthylamine (8.6 g. (0.06 mole) of Eastman Kodak Co., m. p. 109–110°) is placed in a 150-ml. beaker and mixed well with 15 ml. of concentrated hydrochloric acid, and 25 ml. of water is added with stirring. The naphthylamine hydrochloride is then diazotized at 0° by the addition of sodium nitrite (5 g. of sodium nitrite in 10 ml. of water). The diazotized mixture is filtered and the filtrate is transferred to a 500-ml. round-bottom flask immersed in a bath of salt and cracked ice. After the mixture has cooled to approximately −10°, 40 ml. of sodium acetate solution is added drop by drop and with constant stirring. (Care should be exercised to prevent formation of ice.) To this mixture kept at approximately −5°, the alkaline nitromethane solution is now added from the separatory funnel, slowly and with constant stirring. The nitroformazyl separates out as a maroon-colored precipitate, which after standing thirty minutes is separated by filtration with suction (on a Büchner funnel). The crude nitroformazyl is washed thoroughly with water and while still moist is removed to a 150-ml. beaker for purification, as outlined by Bamberger[5] in his synthesis of dithizone. First, 30 ml. of 50% acetic acid is added, gentle heat is applied and the contents are stirred until the temperature of the mixture reaches 40°. It is then cooled to room temperature (stirring meanwhile) and filtered off by suction, the precipitate being washed with 50 ml. of 10% acetic acid followed by water to remove the acid. The air-dried material is then ground in a mortar and treated with 150 ml. of absolute alcohol. The mixture is brought to the boiling point with stirring, after which it is again filtered; the precipitate is washed with about 20 ml. of hot alcohol, sucked dry, and finally air dried.

The nitroformazyl produced is maroon in color and melts at 198–200°. Approximately 7 g. of the nitroformazyl is obtained from 8.6 g. of β-naphthylamine.



Formation of Di-β-naphthylthiocarbazide.—The yield of the nitroformazyl compound is divided into 1-g. portions and one portion is employed at a time. It is treated with 40 ml. of absolute alcohol in an oversized test-tube immersed in an ice-bath. Cylinder ammonia is bubbled through the solution for fifteen to twenty-five minutes and then hydrogen sulfide is passed into the solution, with occasional stirring, until the di-β-naphthylthiocarbazide separates. (The bubbling tube may be used as a stirring rod.) When reduction is complete as indicated by a change of color from maroon to yellow and by disappearance of unreduced particles of the nitroformazyl, 20 ml.

* Presented at the Pittsburgh meeting of the American Chemical Society, September 6, 1943.

(1) I. B. Suprunovich, *J. Gen. Chem.* (U. S. S. R.), **8**, 839–843 (1938).

(2) D. M. Hubbard, *Ind. Eng. Chem., Anal. Ed.*, **12**, 768–771 (1940).

(3) J. Cholak, D. M. Hubbard and R. K. Burkey, *Ind. Eng. Chem., Anal. Ed.*, in press.

(4) E. Fischer, *Ann.*, **190**, 114 (1878); **212**, 316 (1882).

(5) E. Bamberger, R. Padova and E. Omerod, *Ann. Chem.*, 260–307 (1926).

(6) Karl Bambach, and Roland E. Burkey, *Ind. Eng. Chem., Anal. Ed.*, **14**, 904–907 (1942).

TABLE I

INTERMEDIATES IN THE SYNTHESIS OF THIOCARBAZONES BY A MODIFICATION OF BAMBERGER'S METHOD

Starting compd.	Nitroformazyl M. p., °C.	Color	Azide M. p., °C.[a]	Substance produced
Aniline	150–152	Maroon	156–158	Dithizone
o-Toluidine	153–154	Maroon	140–142	Azone
p-Toluidine	160–162	Brick red	145–147	Azone
p-Aminodiphenyl	168–170	Maroon	215–217	Azone
α-Naphthylamine	160–162	Choc. brn.	...	Di-α-naphthylthiocarbazone
β-Naphthylamine	198–200	Maroon	135–137	Di-β-naphthylthiocarbazone
Sulfanilamide	208–210	Orange-red	Not made	.....
p-Bromoaniline	156–158	Brick red	125	Azone[b]
p-Nitroaniline	138–140	Maroon	Not made	.....
Anthranilic acid	Not made			

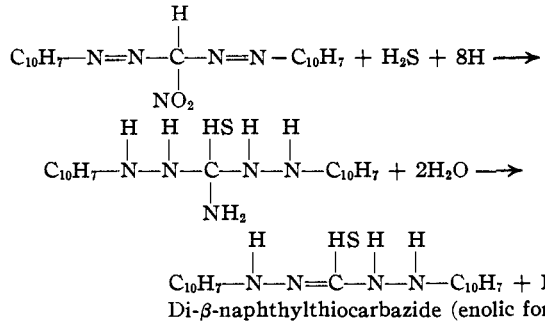
[a] Melting always with decomposition. [b] Soluble in chloroform, but of low tinctorial power; metal ions gave same reaction as with dithizone.

TABLE II

ANALYSES OF THIOCARBAZONES SYNTHESIZED BY A MODIFICATION OF BAMBERGER'S METHOD

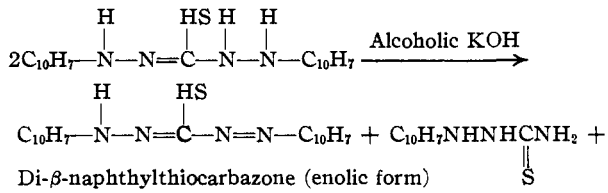
Diarylthiocarbazone	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
Diphenyl-	60.91	61.10	4.72	4.90	21.86	21.49	12.51	12.47
Di-β-naphthyl-	70.79	70.72	4.53	4.62	15.72	15.64	8.99	8.96
Di-α-naphthyl-	70.79	70.68	4.53	4.58	15.72	15.37	8.99	8.96
Di-*p*-diphenyl-	73.40	73.50	4.90	5.05	13.72	13.47	7.85	7.69

of cold water is added with stirring and the mixture is immediately filtered off by suction on a Büchner funnel to remove the di-β-naphthylthiocarbazide.



Di-β-naphthylthiocarbazide (enolic form)[6]

Formation of Di-β-naphthylthiocarbazone.—The carbazide obtained above is treated immediately, while still moist, with 20 ml. of 5% alcoholic potassium hydroxide, at room temperature. It is mixed well and lumps are broken up with the flat end of a stirring rod. A clear dark red solution is obtained and is immediately neutralized with one liter of dilute hydrochloric acid (4 ml. of 6 *N* HCl per 100 ml.). The impure carbazone is filtered off on a Büchner funnel and is air dried.



Di-β-naphthylthiocarbazone (enolic form)

Purification.—The yield of the impure product is again divided into 1-g. portions. One portion is dissolved in 100 ml. of chloroform which has been redistilled from a Pyrex container and treated with hydroxylamine,[6] gentle heat being used to ensure complete solution. The chloroform solution is next transferred to a 150 ml. Squibb-type separatory funnel and is washed with three 25-ml. portions of distilled water, the solution being removed each time to a clean funnel. The washed chloroform solution is now filtered through a fluted paper into a clean glass evaporating dish to remove traces of water and is evaporated to a volume of approximately 10 ml. After cooling to room temperature, 50 ml. of absolute alcohol is added, and the precipitated carbazone is collected on a small filter paper in a Büchner funnel. The collected precipitate is washed once with 10 ml. of absolute alcohol, excess alcohol is drained off by suction, and the precipitate is removed from the paper. Traces of alcohol are removed by evaporation before storage of the final product.

One gram of the nitroformazyl gave an average yield of 0.77 g. of unrefined di-β-naphthylthiocarbazone and approximately 0.2 g. of the purified compound.

Discussion

The procedure outlined above is similar to that used by Bamberger[5] for the synthesis of dithizone from aniline except for the substitution of sodium acetate solution for a portion of the sodium hydroxide solution. The coupling reaction between the diazonium salt of β-naphthylamine and the alkaline nitromethane solution seemed not only to go more smoothly but also produced a nitroformazyl of greater purity and higher yield. Because of the insolubility of the di-β-naphthylthiocarbazone in dilute alkaline ammonia solution, the method of purification usually employed for dithizone[7] could not be used.

Not only has the method described above been used to synthesize dithizone and di-β-naphthylthiocarbazone, but attempts have also been made by varying the starting amines, to synthesize other analogs of these compounds in order to study their reaction with certain metallic ions. The results of these tests are summarized in Table I. Four of the seven carbazones produced were obtained in sufficient amounts to permit purification. In Table II the theoretical elemental composition

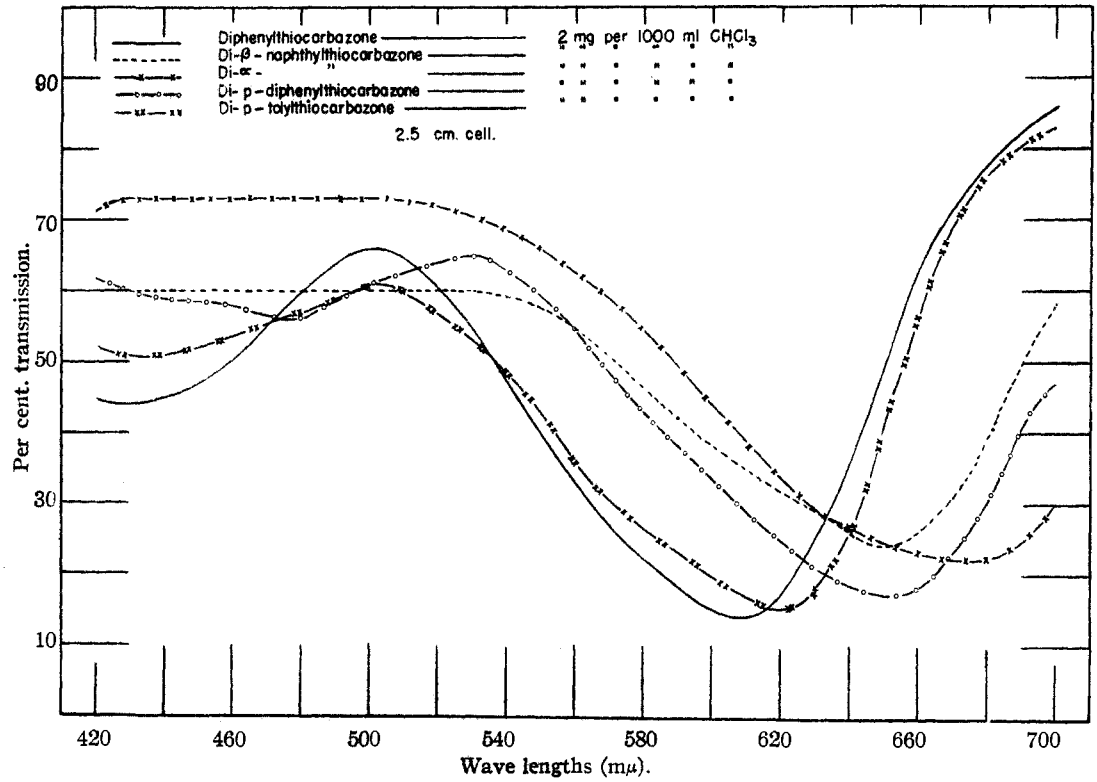

Diphenylthiocarbazone
Di-β-naphthylthiocarbazone
Di-α-
Di-p-diphenylthiocarbazone
Di-p-tolylthiocarbazone
2 mg per 1000 ml CHCl3
2.5 cm. cell.
Per cent. transmission.
90
70
50
30
10
420
460
500
540
580
620
660
700
Wave lengths (mμ).

Fig. 1.

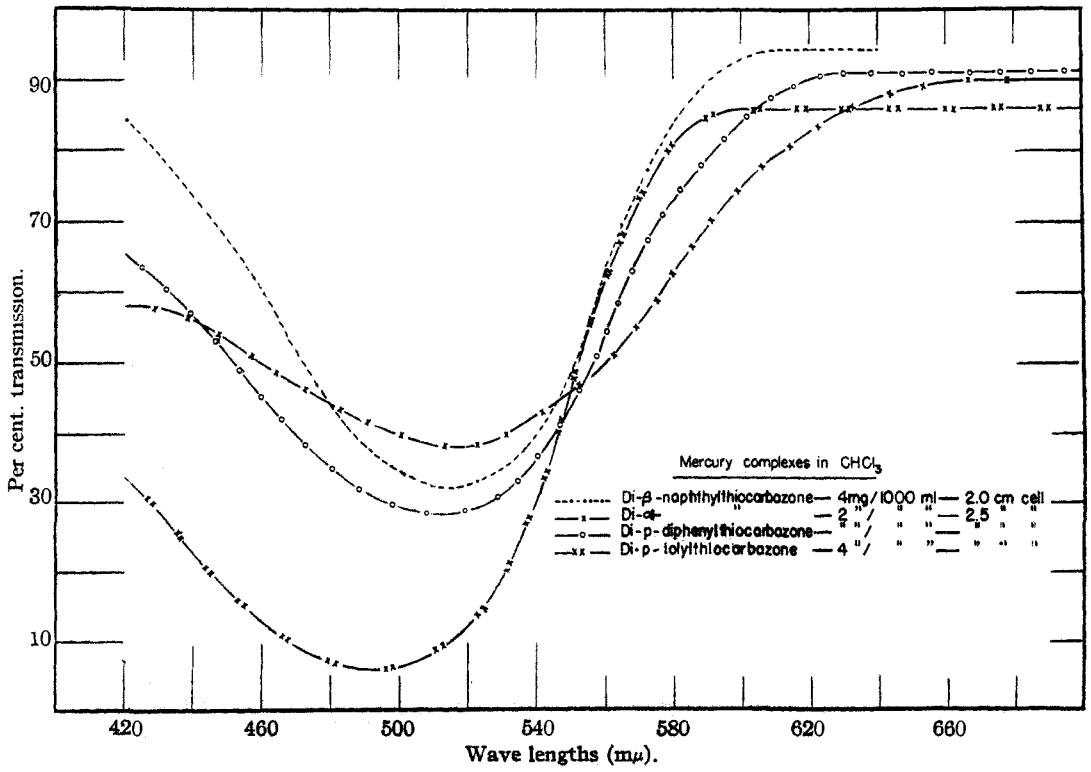

Mercury complexes in CHCl3
Di-β-naphthylthiocarbazone— 4mg/1000 ml— 2.0 cm cell
Di-α- " — 2 " / " " — 2.5 " "
Di-p-diphenylthiocarbazone— " / " " —
Di-p-tolylthiocarbazone — 4 " / " " —
Per cent. transmission.
90
70
50
30
10
420
460
500
540
580
620
660
Wave lengths (mμ).

Fig. 2.

of each of these compounds is compared with that actually obtained on analysis. The dithizone obtained by the above procedure was purified by the method of Clifford and Wichman,[7] the other three by the procedure listed above.

The transmittancy curves for chloroform solutions of five of the carbazones produced are illustrated in Fig. 1. Our studies of these compounds with various metallic ions are not completed, but Fig. 2 gives transmittancy curves for the mercury complexes in chloroform. The mercury dithizonate (not shown) has maximum absorption at 490 mμ while the curves in Fig. 2 in all cases show shifts toward longer wave lengths. Similar shifts were obtained for bismuth and lead[2] and zinc[3] complexes of di-β-naphthylthiocarbazone.

A point of interest in the synthesis described above was that the diphenylthiocarbazide could be isolated as a fairly stable dry compound, whereas the di-β-naphthylthiocarbazide was relatively unstable. When diphenylthiocarbazide was used to produce the carbazone, heat was necessary, whereas with the latter compound the oxidation to carbazone had to be accomplished immediately and without heat.

(7) *Assoc. Official Agr. Chem.*, Official and Tentative Methods, 5th ed., p. 396 (1940).

Summary

The marked superiority of di-β-naphthylthiocarbazone over diphenylthiocarbazone (dithizone) as a microanalytical reagent in the quantitative determination of certain trace metals in biological material, such as mercury and zinc, has brought about the immediate need for a good method for its synthesis.

A new method of synthesis is here reported. It is similar to Bamberger's method for the synthesis of dithizone and was found to be superior to other methods such as that of Suprunovich and an adaptation of it previously reported by one of us.

CINCINNATI, OHIO RECEIVED JULY 9, 1943

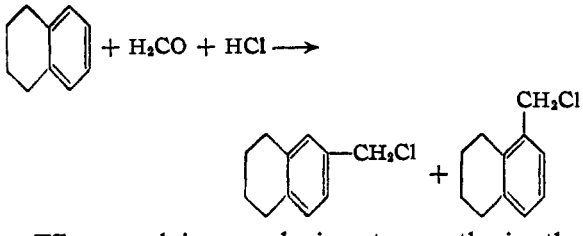
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Chloromethylation of Tetralin. A Synthesis of β-5-Tetralylpropionic Acid

BY RICHARD T. ARNOLD AND RODERICK BARNES

The chloromethylation of tetralin has been effected in several laboratories. Although it is implied in the patent literature[1] that the chloromethyl group is introduced into the 6-position only, most investigators[2,3,4] have claimed the formation of a mixture of isomers. A semiquantitative analysis of this mixture by Vavon and coworkers[4] indicates the presence of 5- and 6-chloromethyltetralins to the extent of 9 and 91%, respectively.

As a result of many experiments we have discovered that the chloromethylation of tetralin can be carried out in such a manner to give a mixture containing more than thirty per cent. of 5-chloromethyltetralin. Although it has not been definitely established we believe that the composition of this mixture depends markedly on the experimental conditions employed.



When used in a malonic ester synthesis, the chloromethylation product from tetralin gave a crude propionic acid (m. p. 75–90°) which after several recrystallizations yielded pure β-5-tetralylpropionic acid (m. p. 136–137°). Dehydrogenation of this acid resulted in the formation of β-1-naphthylpropionic acid. Additional confirmation of the structure assigned to β-5-tetralylpropionic acid was obtained by an independent preparation of β-6-tetralylpropionic acid from 6-propionyltetralin by means of the Willgerodt synthesis.[5]

Cyclization of β-5-tetralylpropionic acid gave 6,7,8,9-tetrahydrobenz[e]indanone-3 which on reduction by Clemmensen's method followed by dehydrogenation gave benz[e]indane.

Upon numerous occasions in this Laboratory we have introduced methyl groups into aromatic nuclei by the catalytic reduction of chloromethyl derivatives. It has been observed frequently that satisfactory results are obtained only when the reduction is attempted shortly after fractionation of the chloromethyl compound. When reduced within a few hours after its preparation, the chloromethylation product from tetralin was hydrogenated quantitatively within twenty minutes to give a mixture of 5- and 6-methyltetralins. If twenty-four hours elapsed between the distillation of the chloromethyltetralin and the reduction experiment, the absorption of hydrogen was sluggish

(1) Lange (I. G. Farbenindustrie), German Patent 533,132.
(2) Darzens and Levy, *Compt. rend.*, 201, 902 (1935).
(3) Martin, *J. Chem. Soc.*, 679 (1941).
(4) Vavon, Bolle and Calin, *Bull. soc. chim.*, [5] 6, 1025 (1939).
(5) This acid (m. p. 81.5–82.5°) was identical with a sample kindly furnished to us by Professor M. S. Newman. See Newman and Zahm, THIS JOURNAL, 65, 1097 (1943).