

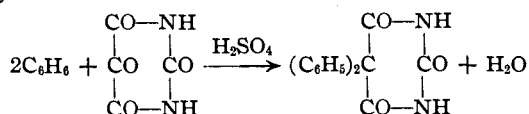
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

5,5-Diphenylbarbituric Acid

By S. M. McELVAIN

In a study of the preparation of 5,5-diarylbarbituric acids, Dox and Thomas¹ found that while it was possible to obtain di-(*p*-hydroxyphenyl)-barbituric acid and di-(3-methyl-4-hydroxyphenyl)-barbituric acid by condensing the corresponding malonic esters with urea in alcoholic sodium ethoxide solution, the diphenylbarbituric acid could not be prepared in this manner. The failure of diphenylmalonic ester to enter into this condensation was later found² to be due to its rapid cleavage into diethyl carbonate and ethyl diphenylacetate by sodium ethoxide, either in the dry state or in alcoholic solution. It was obvious that such behavior made the conventional methods of preparation of the barbituric acids useless for diphenylbarbituric acid.

This paper reports the preparation of diphenylbarbituric acid by a different approach, *viz.*, through the condensation of benzene with alloxan by means of sulfuric acid



This reaction is analogous to that used^{1,2,3} for the preparation of diphenylmalonic ester by the condensation of benzene with oxomalonic ester.

Only relatively small amounts of pure diphenylbarbituric acid, m. p. 290–292°, are obtained from the products of this reaction. The main reaction product is a higher-melting (above 320°) acidic compound, the characterization of which has not been attempted as yet. Fortunately, this material is much more soluble in glacial acetic acid than is diphenylbarbituric acid so that the latter may be obtained pure by repeated crystallizations from this solvent.

Diphenylbarbituric acid crystallizes in fine white needles from glacial acetic acid and yields, on hydrolysis, approximately 95% of the theoretical quantities of ammonia, carbon dioxide and diphenylacetic acid.

Experimental

Alloxan Monohydrate.—This material was prepared by Dr. Kenneth E. Crook in this Laboratory according to the

- (1) Dox and Thomas, *THIS JOURNAL*, **45**, 1811 (1923).
- (2) Cope and McElvain, *ibid.*, **54**, 4319 (1932).
- (3) Cf. also Guyot and Esteve, *Compt. rend.*, **148**, 564 (1909).

following modification of the procedure of Biltz and Heyn.⁴ In a 1-liter 3-necked flask, fitted with an efficient mechanical stirrer, a reflux, a thermometer and gas inlet tube, were placed 100 g. of uric acid, 300 cc. of glacial acetic acid and 50 cc. of water. The contents of the flask were heated, with stirring to 100–105° and a rapid stream of chlorine introduced. During the chlorination the reaction temperature was kept above 100°. At the end of five to seven minutes the original white suspension had changed to a greenish-yellow in color. At this point the amount of chlorine introduced was decreased about one-third and continued until all the solids were dissolved. The total time of chlorination did not exceed ten minutes. The reaction mixture was then cooled in an ice-water bath and the precipitated alloxan monohydrate filtered off and washed with small portions of glacial acetic acid. This crude alloxan monohydrate, which amounted to 55–60 g., was dissolved by pouring over it 1.1 cc. of hot (70°) water for each gram of solid, followed by the addition of an equal volume of boiling glacial acetic acid and the resulting solution was filtered while hot. After filtering, the filtrate was diluted with an equal volume of hot glacial acetic acid, cooled, and allowed to crystallize. The alloxan monohydrate was filtered off, washed with small portions of cold acetic acid, and dried *in vacuo*. The yield was 30–35 g. (31–36% of the theoretical). The melting point of this material is 254–256°.

Diphenylbarbituric Acid.—In a 500-cc. 3-necked flask fitted with a reflux condenser, a mercury seal stirrer and a thermometer in a well, was placed 13 g. of alloxan monohydrate and 60 g. of sulfuric acid, sp. gr. 1.84. Then 75 cc. of benzene was added through the reflux condenser and the mixture heated in an oil-bath, with stirring, for four and one-half hours at 75–80°. After this time the reaction mixture was cooled, most of the benzene layer decanted, and the sirupy sulfuric acid layer poured into 150 cc. of cold water. The precipitated material was filtered off, washed in a beaker with 100 cc. of water and refiltered. After drying in a vacuum desiccator this material weighed 11.4 g. and melted at 260–265°. It was dissolved in 110 cc. of boiling glacial acetic acid, filtered and allowed to crystallize. From this crystallization 5.5 g. of product, m. p. 275–278°, was obtained. After two more recrystallizations from acetic acid in each of which the product was dissolved in about fifteen times its weight of the boiling solvent, 2.0 g. of pure diphenylbarbituric acid, m. p. 290–292° (corr.), was obtained.

Anal. Calcd. for C₁₆H₁₂O₃N₂: C, 68.57; H, 4.28; N, 10.00. Found: C, 68.58; H, 4.19; N, 10.50.

From the mother liquors of these crystallizations, either on standing or by dilution with water, were obtained samples of the material associated with diphenylbarbituric acid. No attempt was made completely to purify this material. Those samples obtained by spontaneous crystallization from the acetic acid mother liquors were found

(4) Biltz and Heyn, *Ann.*, **413**, 60 (1917).

to melt the highest, *viz.*, 320–325°. This material is very insoluble in water but readily soluble in dilute sodium hydroxide solution.

Numerous attempts were made to improve the yield of diphenylbarbituric acid by using stronger sulfuric acid (100% and fuming (20% excess SO₃)) to effect the condensation. Also longer times of reaction were used in some cases. Both of these variations, however, tended to decrease the yields of the barbituric acid and increase the amounts of the associated higher melting material.

Quantitative Hydrolysis of Diphenylbarbituric Acid.—A 1,000-g. sample of diphenylbarbituric acid was boiled for six hours with 40 cc. of 10% potassium hydroxide in a 3-necked flask fitted with an inlet tube for air, a reflux condenser and a dropping funnel. The top of the reflux condenser was attached to another condenser set for downward distillation and which led into a flask containing standard acid. After the six hours of refluxing the water in the reflux condenser was replaced by steam and the ammonia distilled into the standard acid, during which time a slow stream of carbon dioxide- and ammonia-free air was passed through the system. The volume of the hydrolysis solution was maintained by additions of water from the dropping funnel. About 51% of the theoretical amount of ammonia was obtained. The alkaline solution was then refluxed for an additional eight hours and the ammonia distillation repeated. The total amount of ammonia recovered amounted to 0.1147 g. (calcd. 0.1213 g.).

The reaction mixture was then acidified with dilute sulfuric acid from the dropping funnel and the evolved carbon dioxide after drying absorbed in a weighed ascarite bulb. After washing out the system with carbon dioxide-free air the carbon dioxide collected was found to weigh 0.2976 g. (calcd. 0.3144 g.).

The hydrolysis mixture containing the precipitated diphenylacetic acid was treated with solid sodium carbonate until an excess of carbonate was present, filtered to remove

the silica formed from the flask by the long alkaline hydrolysis, and the diphenylacetic acid precipitated from the filtrate with sulfuric acid. This precipitate was filtered off, washed with water and dried. The diphenylacetic acid so obtained melted at 145–147° and weighed 0.71 g. (calcd. 0.75 g.).

The author is indebted to Mr. Fred Beyerstedt for the analyses and quantitative hydrolysis of diphenylbarbituric acid.

Pharmacological Properties.—Diphenylbarbituric acid was tested by Mr. E. E. Swanson of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. The tests were made intraperitoneally in rats. It was found that diphenylbarbituric acid is effective only in very large doses (6–8 times the effective dose of luminal) and that such doses invariably caused the death of the animals.

The pharmacological behavior of diphenylbarbituric acid parallels that reported for di-(*p*-hydroxyphenyl)-barbituric acid by Dox and Thomas,¹ and supports their supposition that barbituric acids which are so essentially aromatic in character would not be effective hypnotics in moderate doses.

Summary

Diphenylbarbituric acid has been prepared by the condensation of benzene with alloxan by means of sulfuric acid. It has been found to be ineffective as an hypnotic in sub-lethal doses.

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The Reactivity of the Halogen in Some Halogenated Nitrobenzenes. I. Reaction with Piperidine¹

BY R. B. SANDIN AND M. LISKEAR

It is a well-known fact that a nitro group in para or ortho position to a halogen in the benzene ring activates the halogen. However, comparatively little attention seems to have been paid in the literature to the combined effect of a para nitro group and one or more ortho halogens, on the reactivity of an aryl halide. One contribution is that of Holleman and De Mooy,² who have carried out quantitative researches on the replacement of substituents in dichloro, nitrochloro and

nitrodichlorobenzenes and have shown that the velocity of replacement of the para halogen in 3,4-dichloronitrobenzene is much greater than in 4-chloronitrobenzene. In this work sodium methylate was used as a reagent for measuring the halogen reactivity.

A very important compound of the above type, *viz.*, 3,4,5-triiodonitrobenzene was used by Harington and Barger³ in their synthesis of thyroxine. In this case it is the para iodine atom which reacts and it was believed by the authors that the meta iodine atoms had something to do with its activa-

(1) This work was supported in part by funds from the Carnegie Corporation Research Grant, for which the authors express their thanks.

(2) Holleman and De Mooy, *Rec. trav. chim.*, **35**, 1–66 (1915).

(3) Harington and Barger, *Biochem. J.*, **21**, 169 (1927).