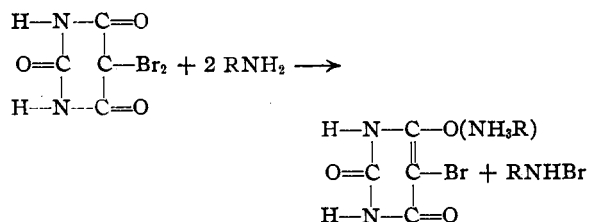


[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF MISSOURI]

Phenyl Nitrogen Substitution and Reactivity in the Barbituric Acid Series<sup>1</sup>

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Dibromobarbituric acid reacts rapidly with primary and secondary amines to form the corresponding amine salt of monobromobarbituric acid.<sup>2</sup> As interpreted by Cope, the reaction may proceed as follows



It reacts with aniline or dimethylaniline to form monobromobarbituric acid and *p*-bromoaniline or *p*-bromodimethylaniline, respectively.<sup>3</sup> With thiourea it forms thiopseudouric acid.<sup>4</sup>

When the halogen derivatives of phenyl nitrogen substituted barbituric acids were used, it was found that the substitution of phenyl groups for hydrogen had a definite effect in the above types of reactions. On the other hand, these nitrogen substituted dibromobarbituric acids both reacted equally well with substituted hydrazines to form hydrazones of the corresponding alloxan, and Macbeth, Nunan and Traill<sup>5</sup> report no difference in the rates of their rapid reaction with hydrazine hydrate.

In the condensation reactions of the methylene group of the barbituric acids with aromatic aldehydes such as cinnamaldehyde and with diphenylformamidine, nitrogen substitution seems to have little if any effect on the rate of the reaction.

## Experimental

The 1-phenyl and 1,3-diphenylbarbituric acids and their halogen derivatives were prepared according to the directions of Whiteley<sup>6</sup> and of Macbeth, Nunan and Traill,<sup>5</sup> with some necessary refinements in their procedures. The phosphorus oxychloride and malonyl chloride methods were both used. Even in the malonyl chloride method, by-products soluble in sodium carbonate solution are

(1) Abstract of a thesis submitted by Lloyd Clayton Morris in partial fulfillment of the requirements for the degree of Master of Arts at the University of Missouri.

(2) Nightingale and Schaefer, *THIS JOURNAL*, **54**, 236 (1932); Cope, *ibid.*, **54**, 1251 (1932).

(3) Conrad and Reinbach, *Ber.*, **35**, 522 (1902); Gupta and Thorpe, *J. Chem. Soc.*, **121**, 1896 (1922).

(4) Trzscinski, *Ber.*, **16**, 1057 (1883).

(5) Macbeth, Nunan and Traill, *J. Chem. Soc.*, 1248 (1926).

(6) Whiteley, *ibid.*, **91**, 3135 (1907).

formed, which are not always completely removed from the barbituric acid by many recrystallizations. This is especially true with 1,3-diphenylbarbituric acid.

In the preparation of the monohalogen derivatives of these barbituric acids, the acid is suspended in dry chloroform, and the 10% solution of bromine in chloroform must be added very slowly and with stirring. The same precautions must be observed in the preparation of the dihalogen barbituric acids, using glacial acetic acid as the solvent. In either preparation, a gummy product results if the bromine is added too rapidly.

**Halogen Barbituric Acids and Aliphatic Amines.**—Dibromobarbituric acid reacts rapidly in warm alcohol solution with butylamine to give a 73% yield of the relatively stable butylamine 5-bromobarbiturate. When 1-phenyl-5,5-dibromobarbituric acid was used in warm or cold absolute alcohol solution, a tar was obtained which would not yield crystals. Benzene was found to be a satisfactory solvent for the reaction. The 1-phenyl-5,5-dibromobarbituric acid (3.6 g.) was dissolved in dry benzene and the solution cooled to +10°. The butylamine (1.5 g.) in a little dry benzene was slowly added with stirring. Some tar formed and adhered to the beaker, but when the benzene was poured off and allowed to stand in the cold for several hours, about 1.2 g. of a mixture of butylamine hydrobromide and the amine barbiturate separated. Attempts to purify this mixture resulted in a tar. Decomposition with the formation of a tar took place when the product was heated above 100° or if it was allowed to come in contact with moist air. Kjeldahl analysis indicated a nitrogen content of 10.97%. Butylamine hydrobromide and butylamine 1-phenyl-5-bromobarbiturate contain 9.11 and 11.80% nitrogen, respectively.

The 5-bromo-1-phenylbarbituric acid and butylamine in benzene under the above conditions gave some tar and a 10 to 15% yield of pure butylamine 5-bromo-1-phenylbarbiturate. The salt is unstable and decomposes to form a red tar at elevated temperatures or if exposed to moist air for any length of time. It melts with decomposition around 110–120°. Other aliphatic amines gave similar results.

*Anal.* Butylamine 1-phenyl-5-bromobarbiturate. Calcd. for  $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_2\text{Br}$ : total N (Kjeldahl), 11.80; amine N, 3.93. Found: N, 11.73; N, 3.91. The amine nitrogen was determined by the procedure used by Cope.

The butylamine 5-bromo-1-phenylbarbiturate was treated with cold sodium carbonate solution in which it readily dissolved, liberating butylamine. The solution was filtered, acidified with hydrochloric acid, and the precipitate which formed collected on a Büchner funnel. This white solid melted at 213° and did not depress the melting point of a sample of 5-bromo-1-phenylbarbituric acid.

Both the mono and dibromo derivatives of 1,3-diphenylbarbituric acid and butylamine under the above conditions gave some tar on evaporation of the solvent but no crystals

of amine barbiturate, even when heated in a sealed tube with or without a solvent. Solvents such as ethyl alcohol and ether as well as benzene were used but with no better results.

When dibenzylamine reacts with dibromobarbituric acid, the crystals which separate rapidly from the alcohol solution are a mixture of the moderately soluble dibenzylamine hydrobromide and dibenzylamine 5-bromobarbiturate. When 1,3-diphenyl-5,5-dibromobarbituric acid was used, the solution turned a violet-red but no crystals separated. Concentration of the solution gave a small amount of colored crystals which on recrystallization were white and melted at 265°. The melting point of these crystals and dibenzylamine hydrobromide was also 265°. Some amine salt of monobromodiphenylbarbituric acid may be formed but is probably too unstable to isolate.

A comparison of rates of reaction of dibromobarbituric acid and 1-phenyl-5,5-dibromobarbituric acid with butylamine is difficult since they require different experimental conditions. Dibromobarbituric acid is only slightly soluble in hot benzene.

**Halogen Barbituric Acids and Aniline.**—Aniline reacts immediately in warm alcohol solution with dibromobarbituric acid to give an almost quantitative yield of *p*-bromoaniline and bromobarbituric acid. The 1-phenyl-5,5-dibromobarbituric acid (3.6 g.) was dissolved in hot alcohol and aniline (1 g.) added. There was no immediate reaction noticeable. After standing for several hours, the precipitate of 1-phenyl-5-bromobarbituric acid (m. p. 213°) which gradually separated was collected on a filter. The *p*-bromoaniline (m. p. 66°) was isolated from the filtrate. Yields were nearly quantitative.

The 1,3-diphenyl-5,5-dibromobarbituric acid and aniline formed some tar, but none of the monohalogen acid separated from the solution, even on long standing and evaporation of the solvent.

**Halogen Barbituric Acids and Thioureas.**—The mono and dibromo derivatives of barbituric acid and of 1-phenylbarbituric acid react rapidly with the thioureas to form the 8-thio-9-R- and 1-phenyl-8-thio-9-R-pseudouric acids, respectively. The halogen barbituric acid (1 mole) in alcohol solution is added to an alcohol solution of the thiourea (1 mole). Heat is evolved and the thiopseudouric acid precipitates rapidly. Yields are nearly quantitative. The thiopseudouric acids are soluble in hot water but insoluble in the common organic solvents, and decompose at their melting points.

#### 8-THIO-9-R-PSEUDOURIC ACIDS

Thiourea used	Formula	°C., dec.	% nitrogen (Kjeldahl) Calcd.	Found
Phenyl	C <sub>11</sub> H <sub>10</sub> N <sub>4</sub> O <sub>3</sub> S	240	20.14	19.90
Allyl	C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> O <sub>3</sub> S	270	23.14	23.16
<i>o</i> -Tolyl	C <sub>12</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> S	275	19.18	19.04

#### 1-PHENYL-8-THIO-9-R-PSEUDOURIC ACIDS

Thiourea	C <sub>11</sub> H <sub>10</sub> N <sub>4</sub> O <sub>3</sub> S	>300	20.14	20.16
Phenyl	C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub> S	280	15.82	15.94
Allyl	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub> S	>300	17.61	17.62

When alcohol solutions of either 5-bromo- or 5,5-dibromo-1,3-diphenylbarbituric acid and the thioureas were mixed, no heat was evolved as with the other halogen barbituric acids, and no crystals separated even after long heating. Evaporation of the solvent gave some crude crystals which, from their nitrogen content and melting points, were apparently mixtures of some of the unchanged halogen barbituric acid and the thiourea. Recrystallization of this material gave the pure thioureas.

**$\alpha$ -Naphthylhydrazine and the Dihalogen Barbituric Acids.**—An alcohol solution of  $\alpha$ -naphthylhydrazine hydrochloride (1 mole) was added to a hot alcohol solution of the nitrogen-substituted dibromobarbituric acid (1 mole). The brick-red hydrazone which separated rapidly was collected on a filter and washed with hot alcohol. These hydrazones are slightly soluble in hot alcohol and insoluble in the other common organic solvents.

Formula	M. p., °C.	% nitrogen (Dumas)		
		Calcd.	Found	
1 - Phenylalloxan $\alpha$ - naphthylhydrazone	C <sub>20</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub>	292	15.64	15.49
1,3 - Diphenylalloxan $\alpha$ -naphthylhydrazone	C <sub>26</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub>	303	12.90	12.96

There was no observable difference in the rates of these reactions.

**Methylene Condensations.**—When either cinnamaldehyde or diphenylformamidine was added to a hot alcohol solution of either 1-phenyl- or 1,3-diphenylbarbituric acid, the slightly soluble cinnamylidene and anilinemethylene derivatives separated rapidly and quantitatively. There was no observable difference in the rate of reaction of a series of mono and diaryl nitrogen-substituted barbituric acids with these reagents.<sup>7</sup>

### Summary

The replacement of one hydrogen by a phenyl group in dibromobarbituric acid decreases the rate of reaction with aniline and possibly with aliphatic amines. The amine salts of 1-phenyl-5-bromobarbituric acid are less stable than those of 5-bromobarbituric acid.

Amines and thioureas do not react appreciably with 1,3-diphenyl-5,5-dibromobarbituric acid under the conditions described.

Aryl nitrogen substitution seems to have little if any effect on the reactivity of the methylene groups in the aryl nitrogen substituted barbituric acids.

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(7) Nightingale and Alexander, *THIS JOURNAL*, **58**, 794 (1936).