CLXI.—*The Labile Nature of the Halogen Atom in Organic Compounds. Part XII. Halogen Compounds of Barbituric Acids.*

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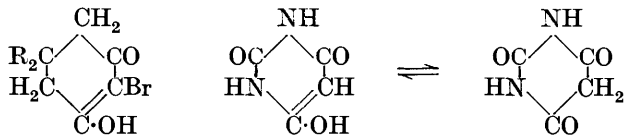
PREVIOUS work on the halogen derivatives of certain diketones has now been extended to compounds of the barbituric acid series. Baeyer (*Annalen*, 1864, **130**, 133) pointed out that there is a difference in the reactivity of the two halogen atoms in dibromobarbituric acid, one being more readily replaced than the other by hydrogen. Whiteley (J., 1921, **119**, 377) extended this observation and found that the reduction of dibromobarbituric acid is effected to the extent of one-half of the total bromine when an aqueous solution of the compound is added to a neutral solution of potassium iodide.

Hydrazine hydrate has now been found to act in a similar way, nitrogen being liberated in a volume agreeing with the reduction of one bromine atom. Similarly the chlorine atom is removed by this reagent from dichlorobarbituric acid. The corresponding halogen compounds of 1-phenylbarbituric acid and 1 : 3-diphenylbarbituric acid, as anticipated, gave results in agreement with the above observations, the reduction occurring readily in all cases.

The stability of the monohalogen derivatives of the barbituric acids may be connected with the enolic constitution of these compounds, in accordance with the explanation advanced (J., 1922, **121**, 1117, 2173) in the case of the derivatives of 1 : 1-dimethyl-*cyclo*hexane-3 : 5-dione and *cyclo*hexane*spirocyclo*hexane-3 : 5-dione (I; $R_2 = Me_2$ and $C_5H_{10}>$, respectively).

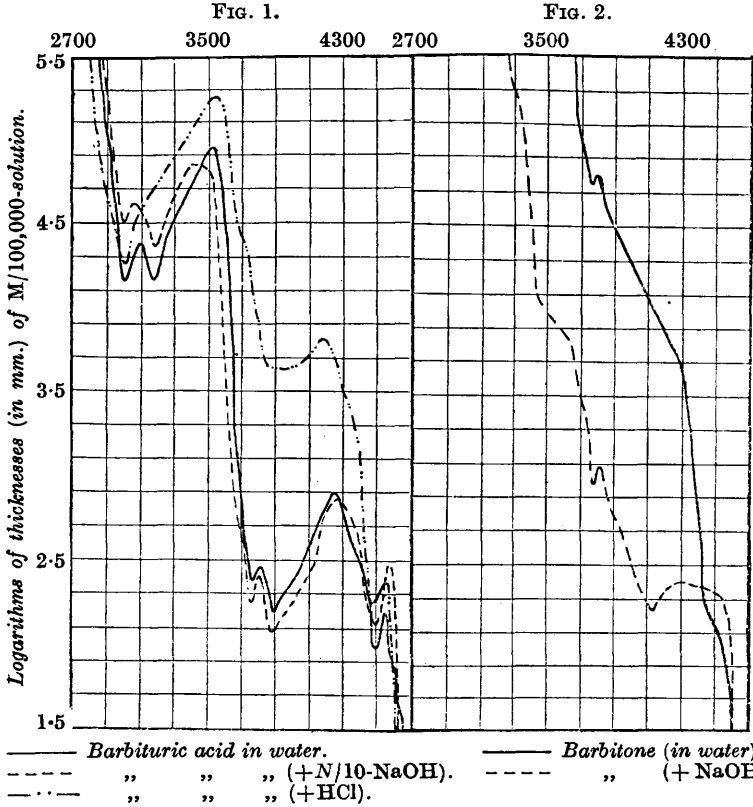


(I.) (II.) (III.)

The difference in behaviour of the dichloro-derivatives of barbituric acids and those of the other diketones previously examined (J., 1922, **121**, 1120, 2176; 1923, **123**, 1129) is of interest. In the former case one of the halogen atoms is eliminated by hydrazine hydrate, whereas in $\gamma\gamma$-dichloroacetylacetone, $\gamma\gamma$-dichlorobenzoylacetone, 4 : 4-dichloro*cyclo*hexane-3 : 5-dione, and *cyclo*hexane*spiro*-4 : 4-dichloro*cyclo*hexane-3 : 5-dione no reduction occurs. A ready explanation of this difference is obtained on the polarity basis by

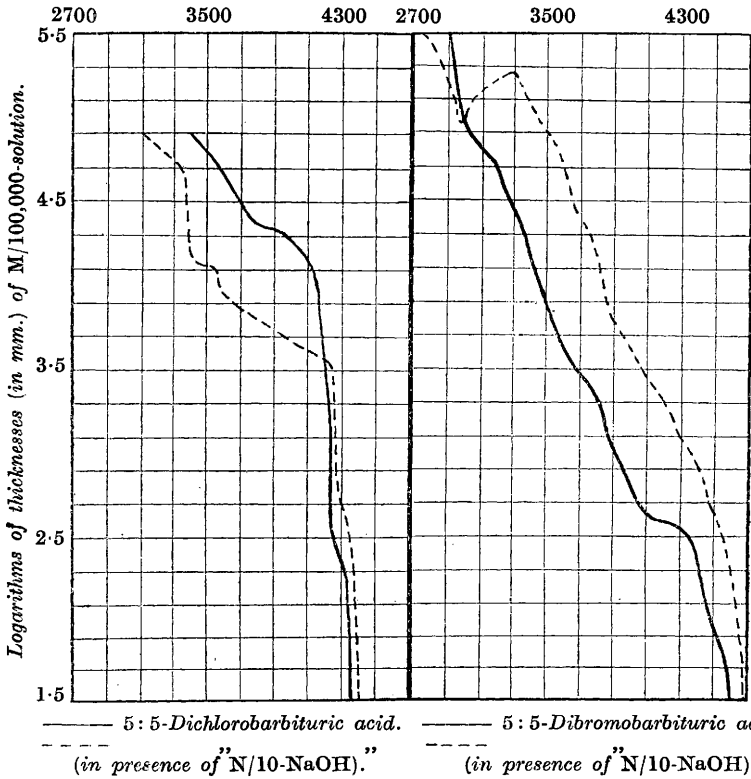
considering the alternate effects of the other atoms in the barbituric acid ring, all of which act together to increase the induced electro-positive character of the halogen atoms.

The stability of the halogen atom in the monohalogenobarbituric acids may, as has been indicated above, be explained by assuming an enolic structure for these compounds. In order to throw further light on this assumption the absorption spectra of characteristic



compounds of this class were examined. The results are shown in Figs. 1—4. The absorption of barbituric acid was examined by Hartley (J., 1905, **87**, 1796), who found that the acid transmitted a continuous spectrum very freely through thicknesses of $M/1000$-solution varying from 1—20 mm. In view of the results obtained in the past few years in absorption work, we were not surprised to find, on further examination of barbituric acid, that it showed selective absorption, its spectrum being characterised by deep complex bands extending over $1/\lambda$ 2950—3400, 3700—4200, 4450—

4530 and with heads at 1/λ 3000, 3170, 3760, 3880, 4490 approximately. The sodium salt (barbituric acid in the presence of $N/10$-sodium hydroxide) shows an absorption practically identical with that of the acid itself and therefore it is evident that in aqueous solution the acid exists in the enolised form (II). As was expected, in the presence of a strong acid the keto-enol change is induced: the absorption curve of barbituric acid in the presence of hydro-



chloric acid does not show to the same extent the marked selective effect characteristic of the enolic structure, the acid being present mainly in the ketonic form (III).

It was considered of interest to examine the absorption of barbitone, as the constitution of this compound is definitely fixed and it may be taken as characteristic of the *C*-dialkyl type. Its spectrum, like that of barbituric acid in the presence of hydrochloric acid, shows no selective effect characteristic of the enolic

form. In the presence of alkali, barbitone further develops the small absorption band at about $1/\lambda$ 3760, and this is probably due to enolisation involving a hydrogen atom of one of the imino-groups.

The absorption spectra of dichloro- and dibromo-barbituric acids are shown in Figs. 3 and 4. The curves are of the same type as those of barbitone, the selective effect connected with the enolic structure being absent. It has been pointed out that hydrazine hydrate reacts with the dihalogen compounds, eliminating one of the halogen atoms and forming the hydrazine salt of the resulting monohalogen derivative. No marked band development is observed in the spectra of the dihalogen compounds on the addition of sodium hydroxide, and therefore it must be inferred that, at the dilutions employed, this reagent does not react greatly with the labile halogen atoms.

The evidence of the absorption spectra of barbituric acid and its derivatives therefore clearly shows (*a*) that the parent acid exists in the enolic form in aqueous solution, whilst in acid solution the compound is present mainly as the ketonic modification; and, further, (*b*) that the dihalogen derivatives are compounds of the *C*-dihalogen type, which leaves no grounds for attributing the reactivity of the halogen atom to an oxygen-halogen linking (compare Graham and Macbeth, J., 1922, **121**, 1109, 2601). The bands found in the regions $1/\lambda$ 3000 and 3760 are probably connected with enolisation involving an imino-group, as these are found in barbitone and dibromobarbituric acid in the presence of alkali.

Experimental.

The absorption spectra recorded were all obtained with a Hilger spectroscope fitted with a camera attachment. The reductions described were carried out in a Van Slyke nitrometer, hydrazine hydrate (50% solution) being employed throughout.

Dichlorobarbituric acid. Barbituric acid, prepared by Gabriel and Coleman's method (*Ber.*, 1904, **37**, 3657), was chlorinated in aqueous suspension at 30—40°, leaflets, m. p. 219—220°, being obtained. The reaction with hydrazine hydrate is vigorous and is complete in a few seconds. 5 C.c. of a solution of 0·980 g. in 25 c.c. of alcohol liberated 11·9 c.c. of nitrogen at 10·5° and 732 mm. One g.-mol. therefore liberates 13·93 g. of nitrogen, corresponding with the removal of one chlorine atom.

The *hydrazide* of monochlorobarbituric acid is precipitated from the above reaction mixture and may also be prepared by the addition of hydrazine hydrate to an alcoholic solution of monochlorobarbituric acid. It does not melt below 300° (Found:

Cl, 18·2; N_2H_4, 16·7.* $C_4H_7O_3N_4Cl$ requires Cl, 18·4; N_2H_4, 16·6%).

Dibromobarbituric acid was prepared by Biltz and Hamburger's method (*Ber.*, 1916, **49**, 635). Recrystallised from 2*N*-nitric acid, it had only a faint rose tinge and melted at 234°. A very vigorous reaction takes place with hydrazine hydrate, and white crystals of the hydrazide of monobromobarbituric acid separate. 5 C.c. of a solution of 1·124 g. of the dibromo-compound in alcohol liberate 12·1 c.c. of nitrogen at 15° and 729·1 mm. One g.-mol. therefore liberates 14·07 g. of nitrogen, which corresponds with the reduction of one bromine atom.

The *hydrazide* of monobromobarbituric acid, isolated above, may also be prepared directly from monobromobarbituric acid. It does not melt below 300° (Found: Br, 33·8; N_2H_4, 13·3. $C_4H_7O_3N_4Br$ requires Br, 34·0; N_2H_4, 13·5%).

Monobromobarbituric acid, prepared by Biltz and Hamburger's method (*loc. cit.*), showed no reduction with hydrazine hydrate at the laboratory temperature.

5 : 5-*Dibromo*-1 : 3-*diphenylbarbituric acid*, prepared by Whiteley's method (J., 1907, **91**, 1367), reacts vigorously with hydrazine hydrate with the elimination of one bromine atom. 0·438 G. of the dibromo-compound liberated 12·6 c.c. of nitrogen at 13° and 719·8 mm. on treatment with hydrazine hydrate. One g.-mol. liberates 14·2 g. of nitrogen, which is in fair agreement with the removal of one halogen atom.

The *hydrazide* of 5-bromo-1 : 3-diphenylbarbituric acid separates during the above reaction as a creamy solid which recrystallises from alcohol in small needle-shaped laths; these appear as arborescent aggregates under the microscope; m. p. 220° (Found: Br, 21·6; N_2H_4, 8·3. $C_{16}H_{15}O_3N_4Br$ requires Br, 21·8; N_2H_4, 8·5%).

5-*Bromo*-1 : 3-*diphenylbarbituric acid*, prepared by Whiteley's method (J., 1921, **119**, 378), was not reduced by hydrazine hydrate, but formed the above hydrazide.

1-*Phenylbarbituric acid* was prepared on lines parallel to those followed in the preparation of the diphenyl acid. Phosphoryl chloride (60 g.), malonic acid (20 g.), and phenylcarbamide (25 g.) were heated under reflux for 6 hours with dry chloroform (200 c.c.) at a temperature just below the boiling point. After removal of the chloroform in a current of air, the residual syrup was left in alcohol to decompose the phosphoryl chloride and then poured on ice. The solution of the creamy solid in sodium carbonate was filtered, and acidified with hydrochloric acid. The resulting solid

* Estimated by a modification of Rimini's method (see J., 1925, **127** 897).

was gently heated with a little alcohol to remove the soluble acetylated products, and after crystallisation from alcohol had m. p. 262° (Found: N, 13·7. $C_{10}H_8O_3N_2$ requires N, 13·7%).

3 : 3-*Dibromo*-1-*phenylbarbituric Acid.* — Phenylbarbituric acid (5 g.) was heated on a water-bath with glacial acetic acid (50 c.c.) * and dissolved on the gradual addition of the theoretical amount of bromine. The solution, after further heating (30 minutes), was poured on ice. Repeated crystallisation of the precipitated yellow solid gave almost white, lath-shaped crystals of the dibromo-acid, m. p. 204° (Found: Br, 44·0. $C_{10}H_6O_3N_2Br_2$ requires Br, 44·2%).

The dibromo-acid reacts readily in alcoholic solution with hydrazine hydrate, liberating nitrogen and precipitating the hydrazide of the monohalogen acid. 0·2980 G. liberated 9·8 c.c. of nitrogen at 16° and 748 mm. One g.-mol. therefore liberates 13·9 g. of nitrogen, which corresponds with the reduction of one bromine atom.

The *hydrazide* of 3-bromo-1-phenylbarbituric acid, isolated above, forms rectangular needles, m. p. 146° (Found: Br, 25·4; N_2H_4, 10·5. $C_{10}H_{11}O_3N_4Br$ requires Br, 25·6; N_2H_4, 10·2%).

5-*Bromo*-1-*phenylbarbituric Acid.*—The calculated quantity of bromine was added to the parent acid (5 g.), suspended in chloroform (50 c.c.) and warmed on the water-bath. After ½ hour, the solution was filtered, and the solid crystallised several times from spirit, being thus obtained in faintly pink, crystalline warts, m. p. 213° (Found: Br, 28·2. $C_{10}H_7O_3N_2Br$ requires Br, 28·2%). No reduction took place on treatment with hydrazine hydrate, the above hydrazide being formed.

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* It is inadvisable to use more acetic acid, as the dibromide is then not precipitated when the solution is subsequently poured on ice.