CCLI.—*The Labile Nature of the Halogen Atom in Organic Compounds. Part XIV. The Reactivity of Halogen Derivatives of 5-Alkylbarbituric Acids.*

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THE difference in reactivity of the two halogen atoms in 5 : 5-di-bromobarbituric acid pointed out by Baeyer (*Annalen*, 1864, **130**, 133) has been supported by the reduction of a series of such acids

by hydriodic acid (Backes, West, and Whiteley, J., 1921, **119**, 377). Macbeth, Nunan, and Traill (J., 1926, 1248) showed that similar considerations hold when hydrazine hydrate is the reducing agent, and that 5 : 5-dichloro-compounds behave in a similar way. Spectroscopic examination proved that the 5-monohalogeno-derivatives existed in the enolic modification, and the stability of such compounds is thus in agreement with other cases, all the substances being characterised by the presence of a double bond at the carbon adjacent to the halogen atom. In the 5-halogeno-5-alkylbarbituric acids the existence of the enolic form is excluded, and reactivity of the halogen atom is therefore to be expected. Easy reduction by hydrazine has been observed in the cases now examined, the reaction taking place quantitatively according to the general equation

$$2RBr + NH_2 \cdot NH_2 = 2RH + 2HBr + N_2.$$
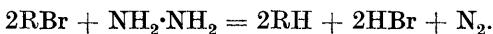
The instability of 5 : 5-dibromobarbituric acids in the presence of platinised electrodes, especially in aqueous-alcoholic solutions (Graham, Macbeth, and Orr, J., 1927, 740), is also shown by the 5-bromo-5-alkylbarbituric acids examined. With polished platinum electrodes, the decomposition of such acids is, in general, slow; and the molecular conductivities may thus be determined. The following values were obtained :

Acid.	Λ_v.	$K \times 10^7$.
5-Bromo-5-methylbarbituric	1·35	1·08
5-Bromo-5-ethylbarbituric	1·95	2·25
5-Bromo-5-n-propylbarbituric	2·06	2·51
5-Bromo-5-isopropylbarbituric	1·82	1·96
5-Bromo-5-butylbarbituric	2·16	2·76
5-Bromo-5-isoamylbarbituric	3·17	2·98

The values of Λ_v given above are the values measured when temperature equilibrium was reached, usually 10—15 minutes after the filling of the conductivity cell. These were considered to be identical with those at zero times, as subsequent change in conductivity was slow. 5-Bromo-5-methylbarbituric acid was exceptional, and extrapolation of the graph of molecular conductivities against time was relied on to give the initial value. The value $\Lambda_\infty^{30°}$ for the series was taken as 412. Trübsack (*Z. physikal. Chem.*, 1895, **16**, 708) gives the value of $\Lambda_\infty^{25°}$ for 5 : 5-dichloro- and 5 : 5-dibromo-barbituric acids as 358 (Siemens units), which corresponds with $\Lambda_\infty^{25°}$ 381 (reciprocal ohms). This agrees with the value for 5-ethyl- and 5 : 5-dimethyl-barbituric acids (International Critical Tables). By applying the Kohlrausch expression for temperature coefficient, $\alpha = 0·0136 + 0·67/(18·5 + L)$ (where α = temperature coefficient, and L = conductivity), separately to the components of Λ_∞ the value of $\Lambda_\infty^{30°}$ was deduced. $\Lambda_\infty^{25°}$ H$^+$ was taken as 347, and

that for the substituted barbituric radical as 34 (381—347). This led to the value $\Lambda^{30°}_\infty$ 412, which was used in the calculation of the dissociation constants by the formula

$$K = \Lambda_v{}^2/(\Lambda_\infty - \Lambda_v)\Lambda_\infty . v.$$

EXPERIMENTAL.

The hydrazine estimations referred to below were carried out in a Van Slyke nitrometer with excess of hydrazine hydrate (50%): the removal of bromine was quantitative in all cases. The conductivity measurements were made in a cell containing polished platinum electrodes (cell constant 0·1555). All conductivities were determined at 30°, the specific conductivity of $N/50$-potassium chloride at this temperature being taken as $3·036 \times 10^{-3}$.

5-Methylbarbituric acid was prepared by a modification of Fischer and Dilthey's method (*Annalen*, 1904, **335**, 355). Sodium (20 g.) in alcohol (250 c.c.) and ethyl methylmalonate (50 g.) and urea (26 g.) were heated in a pressure bottle at 110° for 3 hours. The filtrate obtained after cooling was repeatedly washed with alcohol, dissolved in hot water, and acidified. 5-Methylbarbituric acid crystallised on cooling, and was twice recrystallised from water and finally from water–alcohol. M. p. 198°.

5-*Bromo*-5-*methylbarbituric acid.* Bromine was gradually added to the parent acid (5 g.) in hot water (50 c.c.) until a permanent colour was produced. The bromo-compound, which crystallised on cooling, was recrystallised from hot water and dried in a desiccator. Yield, 75%; m. p. 190°.

On treatment with hydrazine hydrate the bromo-compound (0·2348 g.) liberated nitrogen quantitatively (13·2 c.c. at 20° and 744·3 mm.). The *hydrazide* of 5-methylbarbituric acid separated from the reaction mixture as flat rectangular plates, m. p. 240° (decomp., complete at 245°) [Found: N (hydrazine), 16·0. $C_5H_{10}O_3N_4$ requires N, 16·1%].

In the reduction of the other 5-bromo-5-alkyl acids examined, the hydrazides were too soluble to separate in the nitrometer.

The following conductivities ($M/100$-solution) were observed, and were used graphically to determine the initial conductivity of the bromo-acid.

Resistance	11,430	11,160	11,040	10,600	9820	9440	8680	7730	7050
Mol. cond.	1·36	1·39	1·41	1·47	1·59	1·65	1·79	2·01	2·21
Time (mins.)	5	10	15	30	65	80	120	180	240

5-Ethylbarbituric acid was prepared in the same way as the methyl acid, but the yields obtained were not so good as those recorded by Volwiler (*J. Amer. Chem. Soc.*, 1925, **47**, 2236).

5-*Bromo*-5-*ethylbarbituric acid*, m. p. 202°, was prepared in 77% yield by direct bromination of the parent acid in hot water (Found : Br, 33·8. $C_6H_7O_3N_2Br$ requires Br, 33·9%).

The bromo-compound (0·279 g.) on reduction by hydrazine liberated 14·2 c.c. of nitrogen at 19° and 749·3 mm.

The conductivity measurements show a change in the molecular conductivity ($M/100$-solution) from the initial value 1·95 to 2·10 after 5 hours.

5-Propylbarbituric acid was prepared by heating under pressure at 110° for 3 hours a mixture of sodium (17 g.) in alcohol (300 c.c.) with urea (22·5 g.) and ethyl propylmalonate (50 g.). The yield was of the same order as those obtained by Fischer and Dilthey (*loc. cit.*) and Volwiler (*loc. cit.*).

5-*Bromo*-5-*propylbarbituric acid* was obtained in practically quantitative yield when the parent acid (8 g.), suspended in warm water (100 c.c.), was gradually treated with excess of bromine. The excess of bromine was removed by boiling, and white crystals of the bromo-compound separated on cooling. Recrystallised from water, it had m. p. 163·5° (Found : Br, 32·1. $C_7H_9O_3N_2Br$ requires Br, 32·1%).

The bromo-compound (0·2105 g.) on reduction liberated 10·3 c.c. of nitrogen at 17·1° and 744 mm.

The molecular conductivity ($M/100$-solution) showed a change from an initial value of 2·02 to 2·25 after 15 hours.

5-*Bromo*-5-iso*propylbarbituric acid*. The parent acid was prepared in 75% yield by a method similar to those described above. The *bromo*-derivative was obtained in 85% yield by direct bromination of the parent acid suspended in warm water. It crystallised from water in small white prisms, m. p. 163° (Found : Br, 32·0. $C_7H_9O_3N_2Br$ requires Br, 32·1%).

0·2295 G. on treatment with hydrazine yielded 11·3 c c. of nitrogen at 18° and 737 mm.

The molecular conductivity ($M/100$-solution) is lower than that of the corresponding n-propyl derivative, and changes from an initial value of 1·74 to 1·83 after 4 hours.

5-*Bromo*-5-n-*butylbarbituric acid*. The parent acid was prepared by heating under reflux the required reagents (Volwiler, *loc. cit.*), but our yield never exceeded 54%. Better results (74% yield) were obtained when the reaction was carried out under pressure at 115° for 3 hours. In the bromination we were unable to obtain satisfactory results with methyl alcohol as a solvent (*J. Amer. Chem. Soc.*, 1922, **44**, 1564, 1578), but the reaction gave moderately good yields when bromine was gradually added to a suspension of the parent acid in warm water (30—40°). The product was repeatedly

crystallised from alcohol–water, but the m. p. 109° did not agree
with that (114°) previously recorded (Found : Br, 30·3. Calc. for
$C_8H_{11}O_3N_2Br$: Br, 30·4%).

0·271 G. of the bromo-compound on reduction liberated 12·6 c.c.
of nitrogen at 18° and 744 mm.

The molecular conductivity (M/100-solution) was 2·14.   5-*Bromo*-
5-iso*amylbarbituric acid*.   The parent acid was obtained in more
than 50% yield by a pressure method similar to those employed
above.   The parent acid (10 g.), dissolved in much warm water,
was treated with excess of bromine.   On cooling, the *bromo*-deriv-
ative separated in long silky needles, m. p. 175° after recrystallis-
ation from dilute alcohol (yield, 90%) (Found : Br, 28·9.
$C_9H_{13}O_3N_2Br$ requires Br, 28·85%).

0·303 G. of the bromo-compound when reduced by hydrazine
liberated 13·4 c.c. of nitrogen at 17·5° and 738·7 mm.

The molecular conductivity (M/200-solution) varied from an
initial value of 3·16 to 3·30 after 6 hours.

5-*Bromo*-1 : 3-*diphenyl*-5-*benzylbarbituric   acid*.   1 : 3-Diphenyl-
barbituric acid (Whiteley, J., 1907, **91**, 1342) was dissolved (4 g.)
in glacial acetic acid (40 c.c.) on the water-bath, and excess of
bromine (1·6 g.) in glacial acetic acid added ; after a few minutes
the *bromo*-derivative began to separate.   The mixture was poured
on ice, and the precipitated acid recrystallised from chloroform–
alcohol, forming white micro-crystalline octahedra, m. p. 195°,
sparingly soluble in hot alcohol, and easily soluble in chloroform
(Found : Br, 17·6. $C_{23}H_{17}O_3N_2Br$ requires Br, 17·8%).

0·425 G. of the bromo-acid on treatment with hydrazine gave
11·6 c.c. of nitrogen at 16·5° and 751·5 mm.   This corresponds with
14·3 g. of nitrogen per g.-mol., and the reaction may be regarded as
quantitative within the limits of experimental error.

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