

XCI.—*The Influence of Groups and Associated Rings on the Stability of Certain Heterocyclic Ring Systems. Part I. The Substituted Glutarimides.*

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THE modified strain theory developed by Thorpe and Ingold to explain the relative stabilities of various ring systems has on the whole received ample general experimental confirmation by the work of these and other workers. Their investigations, however, with few exceptions, involved experimental conditions of such a drastic nature that the quantitative comparison of the stabilities of the various systems was a matter of considerable difficulty, and frequently corrections had to be applied for one or more side-reactions which were difficult to control. Though these phenomena were successfully unravelled by these chemists, the difficulty in the

way of the ideal solution of the problem could not fail to be noticed. This difficulty was partly solved by Ingold, Sako, and Thorpe (J., 1922, 121, 1177) by studying the hydrolysis under mild conditions of a number of substituted hydantoins; but the necessary variety of substituted hydantoins is not easy to obtain. Moreover, although the work on hydantoins brought forward strong evidence in support of the modified strain theory, it seemed remarkable that the influence of the substituents was completely unaffected by the presence of two nitrogen atoms in the ring, the valency direction of each of which could not fail to be affected in the same way by the substituents. In other words, the disturbing factors introduced by the nitrogen atoms and the carbonyl groups made the problem more complicated than was desirable.

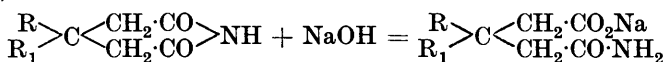
It was considered that heterocyclic rings, such as imides, anhydrides, and lactones, which are opened under mild conditions without complicated side-reactions, would be more suitable for a quantitative study of ring stability. Although a considerable amount of work has been done on the stability of anhydrides by Voermann, Rivett and Sidgwick, Böeseken and his collaborators, and by Verkade and Hjelt, it affords no substantial contribution towards a solution of the present problem.

Sporadic studies of the hydrolysis of a few imides by Miolati (*Atti R. Accad. Lincei*, 1894, 3, i, 515; 1896, 5, ii, 375) and of a few lactones by Hjelt (*Ber.*, 1891, 24, 1236) and by Henry (*Z. physikal. Chem.*, 1892, 10, 96) throw but little light on the subject under discussion.

The method employed by Miolati and by Henry has now been utilised to work out the comparative rates of hydrolysis of the ring systems mentioned above. It is hoped that by studying the various combinations of the carbon atoms, the carbonyl group, and the hetero-atom, some information may be obtained on the actual effect of the substituting hydrocarbon radicals unaffected by other factors.

The evidence thus obtained from the hydrolysis experiments points unmistakably to the well-marked influence of the substituents in modifying the stability of the various systems in the direction indicated by the modified strain theory. The fact that the ring opens at the hetero-atom, and not at any of the carbon atoms of the ring, probably diminishes the effective manifestation of the molecular strain contributed, if at all, by the distortion of the bonds of the nitrogen or the oxygen atom, unless we assume that the bonds of atoms with "residual valency" may be of a more pliant and accommodating nature than carbon bonds are known to be. This discussion will be amplified, however, in a future communication.

The present paper is concerned with a study of the velocity of hydrolysis of a number of substituted glutarimides, the various substituents being H,H; Me,H; Et,H; Me,Me; Me,Et; Et,Et; *cyclopentane*, and *cyclohexane*. In the presence of dilute caustic soda, the reaction



was found to be bimolecular, having a suitable velocity at 25°. Complications due to side reactions took place if the reaction was prolonged beyond the early stages. Another disturbing factor is the presence in the imide of traces of the free acid, which in the form of its salt has a great catalytic influence on the hydrolysis, the velocity being increased at a rate out of all proportion to the amount of the impurity. This factor was responsible for a number of anomalous results in the preliminary experiments, but was eliminated by more thorough purification of the imides.

The following table shows how closely the experimental data agree with the expectations of the modified strain theory, and also indirectly justifies the method here adopted. The full significance of the actual coefficients is not easy to explain. In the table, 2θ represents the calculated angle between two of the carbon bonds and k represents the velocity coefficients of the reactions.

Substituents.	2θ .	$10k$.	Substituents.	2θ .	$10k$.
H,H	115.3°	0.247	Me,Et	?	0.0124
Me,H	112.5	0.0725	Et,Et	?	0.00435
Et,H	?	0.158	<i>cyclopentane</i>	107.2°	0.00275
Me,Me	109.5	0.0127	<i>cyclohexane</i>	105.2	0.00215

EXPERIMENTAL.

Preparation of the Imides.—All the imides were prepared by distilling the dry ammonium salt of the appropriate acid from a small retort under ordinary pressure. A large, smoky flame was used and superheating was avoided, the imides being thus obtained in good yield. They were purified by crystallisation from acetone-ether, and then from hot water, being undecomposed by such treatment. Most of the imides are known, but the di-substituted ones had not previously been prepared by the above method. The m. p.'s of the already-known imides agreed completely with those recorded in the literature. As all the glutaric acids are known, details of their preparation are omitted.

Hydrolysis.—95 C.c. of a $N/190$ -solution of the imide (actual weights shown at the head of each table) were placed in a 300 c.c. flask and kept in a thermostat at 25° ($\pm 0.2^\circ$). When the solution had attained the temperature of the thermostat, 5 c.c. of $N/10$ -sodium hydroxide solution were introduced by means of a pipette

and the mixture was well stirred. After 1 minute, portions of 10 c.c. were removed at intervals of 5—10 minutes (depending on the velocity of the reaction), run into about 15 c.c. of ice-cold distilled water, and the unused alkali was titrated with $N/100$ - or $N/200$ -sulphuric acid. The velocity coefficient was calculated from the formula for a bimolecular reaction $k = x/ta(a - x)$, where t is the time (in minutes), a the initial concentration of imide (corresponding to 10 c.c. of $N/200$ -, or 5 c.c. of $N/100$ -acid), and x the alkali utilised. No great accuracy is claimed where the velocity is high, but the number of such cases is small. The results of the experiments are given in the Tables I—VIII, the figures in the second column representing c.c. of $N/100$ - (or $N/200$ -) acid used in the titration.

Glutarimide (see Table I).—Yield, 65.4%. It was crystallised first from acetone and then from water; glistening scales, m. p. 152° (Found: N, 12.1. Calc.: N, 12.4%).

TABLE I.

0.1486 g. dissolved in 250 c.c.;
 $a = 5.0$.

t .	$a - x$.	k .
0	4.2	—
5	2.2	0.0254
10	1.5	0.0233
15	1.05	0.0256
20	0.95	0.0244
27	0.65	0.0248
33	0.55	0.0243

Mean 0.0247

(Miolati obtained 0.0251.)

TABLE II.

0.1672 g. dissolved in 250 c.c.;
 $a = 5.0$.

t .	$a - x$.	k .
0	4.6	—
5	3.5	(0.0086)
10	2.95	0.0070
15	2.4	0.0072
20	2.05	0.0072
25	1.75	0.0074
30	1.5	0.0074

Mean 0.00725

β -*Methylglutarimide* (see Table II).—Yield, 68%; crystallised from ether-acetone in scales, m. p. 142—143° (Found: N, 11.3. Calc.: N, 11.0%).

β -*Ethylglutarimide* (see Table III).—Yield, 57%; crystallised from acetone-ether and then from water; scales, m. p. 87° (Found: N, 10.3. Calc.: N, 9.9%).

TABLE III.

0.0742 g. dissolved in 100 c.c.;
 $a = 5.0$.

t .	$a - x$.	k .
0	3.2	—
5	2.4	(0.0216)
10	1.8	0.0177
15	1.425	0.0167
20	1.25	0.0166
25	1.05	0.0150
30	0.90	0.0133
35	0.825	0.0192

Mean 0.0158

TABLE IV.

0.1854 g. dissolved in 250 c.c.;
 $a = 5.0$.

t .	$a - x$.	k .
0	4.85	—
5	4.05	—
10	4.40	0.00136
15	4.15	0.00136
20	3.95	0.00133
25	3.75	0.00133
30	3.7	0.00117
43	3.45	0.00104

Mean 0.00127

$\beta\beta$ -*Dimethylglutarimide* (see Table IV).—Yield, 75%; crystallised from water in long needles, m. p. 147° (Found: N, 10.3. $C_7H_{11}O_2N$ requires N, 9.9%).

$\beta\beta$ -*Methylethylglutarimide* (see Table V).—Yield, 70%; crystallised from water in leafy plates, m. p. 127° (Found: N, 9.3. $C_8H_{13}O_2N$ requires N, 9.0%).

TABLE V.

0.0816 g. dissolved in 100 c.c.;
 $a = 5.0$.

<i>t.</i>	$a - x.$	<i>k.</i>
0	4.8	—
5	4.7	0.00127
10	4.4	0.00136
15	4.2	0.00127
20	3.95	0.00132
25	3.8	0.00126
30	3.7	0.00117
35	3.65	0.00105

Mean 0.00124

TABLE VI.

0.0846 g. dissolved in 95 c.c.;
 $a = 5.0$.

<i>t.</i>	$a - x.$	<i>k.</i>
0	4.95	—
5	4.85	(0.000618)
10	4.8	0.000416
20	4.6	0.000434
30	4.45	0.000412
40	4.2	0.000476
50	4.1	0.000439

Mean 0.000435

$\beta\beta$ -*Diethylglutarimide* (see Table VI).—Yield, 48%; crystallised in glistening plates from water; m. p. 146—147° (Found: N, 8.0. $C_9H_{15}O_2N$ requires N, 8.2%). Owing to its sparing solubility, 0.0846 g. (corresponding to 95 c.c. of *N*/190-solution) of the finely powdered imide was suspended in 95 c.c. of distilled water and kept at 25°; 5 c.c. of *N*/10-sodium hydroxide solution were added, and the imide then dissolved in 5 minutes.

cycloPentanediacetimide (see Table VII).—Yield, 68%; crystallised in plates from acetone or water, m. p. 153—154° (Found: N, 8.2. $C_9H_{13}O_2N$ requires N, 8.4%).

TABLE VII.

0.2198 g. dissolved in 250 c.c.;
 $a = 5.0$.

<i>t.</i>	$a - x.$	<i>k.</i>
0	5.1	—
5	4.90	—
10	4.85	0.000309
20	4.75	0.000263
30	4.65	0.000252
40	4.55	0.000297
50	4.425	0.000261
60	4.3	0.000271

Mean 0.000275

TABLE VIII.

0.1814 g. dissolved in 95 c.c.;
 $a = 5.0$.

<i>t.</i>	$a - x.$	<i>k.</i>
0	5.0	—
5	4.85	—
10	4.85	0.000309
20	4.8	0.000209
30	4.7	0.000212
40	4.6	0.000217
50	4.5	0.000220
60	4.425	0.000216

Mean 0.000215

cycloHexanediacetimide (see Table VIII).—Yield, 70%; crystallised from water in glistening scales, m. p. 169° (Found: N, 7.5. $C_{10}H_{15}O_2N$ requires N, 7.7%).

Summary.

The velocity coefficients for the hydrolysis of a number of substituted glutarimides have been studied with the view of finding how far the order of stability in this series of compounds agreed with the expectations of Thorpe and Ingold's modified strain theory. The agreement is quite satisfactory. The unusual instability of glutarimide itself is very marked, and the effect of the methyl group in increasing the stability is also remarkable. After that, however, there is a steady increase of stability as the series is ascended (H,H; Me,H; Et,H; Me,Me; Me,Et; Et,Et; *cyclopentane*; *cyclohexane*).

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