453. *The Relationship of Structure to Activity in Plant Growth-regulating Compounds. Part I. Rates of Alkaline Hydrolysis of Substituted 2,4-Dichlorophenoxyacetamides.*

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A number of *N*-substituted 2,4-dichlorophenoxyacetamides have been prepared. The rates of hydrolysis of these compounds by $0.22N$-alcoholic alkali have been determined. In this way these compounds can be ranked in order of chemical stability and according to the electron availability on the carbon atom of the amide group, which is the point of attack of the hydroxyl ion during hydrolysis.

IN the course of an investigation into the plant growth-regulating activities of various derivatives of 2,4-dichlorophenoxyacetic acid it was noted that certain closely related *N*-substituted amides show considerable variation in plant growth-regulating activity. Wain and his co-workers [1] consider that the amides of active plant-growth regulating acids are not active as such but are first hydrolysed in the plant to the free acid. If this should be the case there will be a correlation between the rates of hydrolysis within the plant and the growth-regulating activities of the compounds. The mechanism and rate of hydrolysis, within the plant, of foreign substances is difficult to establish. As a preliminary measure of the chemical stability of such compounds, the rates of alkaline hydrolysis of a number of *N*-substituted 2,4-dichlorophenoxyacetamides were determined.

EXPERIMENTAL

Preparation of the Amides.—The amides were prepared by standard methods as follows.

Method 1. Recrystallised 2,4-dichlorophenoxyacetic acid was heated with a 50% molar excess of amine at 150—160° until evolution of water ceased. The excess of amine was removed by dilute hydrochloric acid and the product was crystallised.

Method 2. The appropriate amine was treated with 2,4-dichlorophenoxyacetyl chloride in the presence of a small excess of aqueous base.

Method 3. *N*-Methyl-*N*-phenyl-2,4-dichlorophenoxyacetamide (16) was prepared by methylating 2,4-dichlorophenoxyacetanilide with methyl iodide in acetone by Pachter and Kloetzel's method.[2]

[1] Wain and Wightman (Ed.), " The Chemistry and Mode of Action of Plant Growth Substances," Butterworths, London, 1956, pp. 187, 234.
[2] Pachter and Kloetzel, *J. Amer. Chem. Soc.*, 1952, **74**, 1321.

Method 4. The amino-anilides (10 and 11) were prepared by hydrogenating the corresponding nitroanilides over Raney nickel in dioxan at room temperature and pressure.

The following 2,4-dichlorophenoxyacetamides were prepared by these methods: (1) 2,4-Dichlorophenoxyacetamide,[3] method 2, needles, m. p. 155° (Found: N, 6·2. Calc. for $C_8H_7Cl_2NO_2$: N, 6·4%). (2) N-*Methyl*, method 2, needles, m. p. 110—110·5° (Found: C, 46·1; H, 3·9. $C_9H_9Cl_2NO_2$ requires C, 46·2; H, 3·9%). (3) N-*Ethyl*, method 2, needles, m. p. 108—108·5° (Found: C, 48·4; H, 4·4. $C_{10}H_{11}Cl_2NO_2$ requires C, 48·4; H, 4·4%). (4) N-*Isopropyl*, method 2, needles, m. p. 125—125·5° (Found: C, 50·4; H, 4·8. $C_{11}H_{13}Cl_2NO_2$ requires C, 50·4; H, 5·0%). (5) *N*-2'-*Hydroxyethyl*,[4] method 2, needles, m. p. 121·5—122·5° (Found: C, 45·2; H, 4·05. Calc. for $C_{10}H_{11}Cl_2NO_3$: C, 45·5; H, 4·2%). (6) *N*-Phenyl,[5] method 1, needles, m. p. 109—110° (Found: N, 4·6. Calc. for $C_{14}H_{11}Cl_2NO_2$: N, 4·7%). (7) N-p-*Tolyl*, method 1, needles, m. p. 140·5° (Found: N, 4·3. $C_{15}H_{13}Cl_2NO_2$ requires N, 4·5%). (8) *N-p*-Nitrophenyl,[6] method 1, plates, m. p. 202—203·5° (Found: C, 49·6; H, 3·0. Calc. for $C_{14}H_{10}Cl_2N_2O_4$: C, 49·3; H, 2·9%). (9) N-m-*Nitrophenyl*, method 1, needles, m. p. 200—201° (Found: C, 49·2; H, 3·0%). (10) *N-p*-Aminophenyl,[6] method 4, needles, m. p. 140—143° (Found: C, 53·9; H, 3·9. Calc. for $C_{14}H_{12}Cl_2N_2O_2$: C, 54·0; H, 3·9%). (11) N-m-*Aminophenyl*, method 4, needles, m. p. 132·5—135° (Found: C, 53·9; H, 3·9%). (12) N-p-*Chlorophenyl*, method 2, needles, m. p. 155·5—156° (Found: C, 50·7; H, 3·1. $C_{14}H_{10}Cl_3NO_2$ requires C, 50·8; H, 3·0%). (13) N-3,4-*Dichlorophenyl*, method 2, needles, m. p. 166·5—167° (Found: C, 45·9; H, 2·5. $C_{14}H_9Cl_4NO_2$ requires C, 46·0; H, 2·5%). (14) N,N-*Dimethyl*, method 2, needles, m. p. 110·5—111·5° (Found: C, 48·0; H, 4·5. $C_{10}H_{11}Cl_2NO_2$ requires C, 48·4; H, 4·4%). (15) NN-*Bis*-2-*hydroxyethyl*, method 2, rhombs, m. p. 98—99·5° (Found: C, 46·3; H, 4·9. $C_{12}H_{15}Cl_2NO_4$ requires C, 46·75; H, 4·9%). (16) N-*Methyl-N-phenyl*, method 3, needles m. p. 119·5—120° (Found: C, 58·3; H, 4·1. $C_{15}H_{13}Cl_2NO_2$ requires C, 58·1; H, 4·2%). (17) NN-*Diphenyl*, method 2, needles, m. p. 124·5—125° (Found: C, 64·5; H, 4·0. $C_{20}H_{15}Cl_2NO_2$ requires C, 64·5; H, 4·0%).

Rates of Hydrolysis of the Amides.—*Procedure 1; bases insufficiently strong to interfere in direct titration.* Approximately 0·01 mole of the amide was weighed into a flask, followed by 100 ml.

Rates of hydrolysis of 2,4-dichorophenoxyacetamides, determined in 0·22N-*potassium hydroxide in alcohol containing* 10% *v/v of water.*

Compd. No.	$Cl_2C_6H_3 \cdot O \cdot CH_2 \cdot CO \cdot NRR'$ R	R'	Temp. (° c)	10^3k (min.$^{-1}$)	$t_{\frac{1}{2}}$ (50°) (min.)
1	H	H	40	7·8 ± 0·83	90 ± 9·4 [b]
1	H	H	50	14 ± 1·9	50 ± 6·8
2	H	Me	50	2·1 ± 0·10	330 ± 14
3	H	Et	50	0·98 ± 0·085	710 ± 52
4	H	Pr^i	50	0·12 ± 0·0050	5800 ± 170
5	H	$CH_2 \cdot CH_2 \cdot OH$	50	3·1 ± 0·11	220 ± 7·9
6	H	Ph	50	2·7 ± 0·14	260 ± 10
7	H	C_6H_4Me-p	50	2·1 ± 0·14	330 ± 22
8	H	$C_6H_4 \cdot NO_2-p$	50	— [a]	<20
9	H	$C_6H_4 \cdot NO_2-m$	50	9·7 ± 0·69	72 ± 5·1
10	H	$C_6H_4 \cdot NH_2-p$	50	2·8 ± 0·21	250 ± 19
11	H	$C_6H_4 \cdot NH_2-m$	50	3·8 ± 0·42	185 ± 20
12	H	C_6H_4Cl-p	50	3·6 ± 0·12	190 ± 6·5
13	H	$C_6H_3Cl_2-3,4$	50	6·7 ± 0·65	100 ± 10
14	Me	Me	50	14 ± 1·5	50 ± 5·5
15	$CH_2 \cdot CH_2 \cdot OH$	$CH_2 \cdot CH_2 \cdot OH$	50	— [a]	<20
16	Me	Ph	50	5·2 ± 0·30	130 ± 7·7
17	Ph	Ph	40	~20	~30 [b]

[a] Reaction was too rapid to be followed by method employed.   [b] $t_{\frac{1}{2}}$ values at 40°.

of alcohol containing 20% of water by volume. When the flask and the corresponding blank had reached the thermostatically controlled equilibrium temperature 100 ml. of 0·45N-alcoholic potassium hydroxide were added rapidly. Samples were taken immediately from each flask, the test sample being chilled rapidly to stop reaction. Aliquot portions of test and blank

[3] Synerholm and Zimmerman, *Contribn. Boyce Thomson Inst.*, 1947, **14**, 369.
[4] Newman, Fones, and Renoll, *J. Amer. Chem. Soc.*, 1947, **69**, 718.
[5] Maruyama and Moriwaki, *J. Agric. Chem. Soc. Japan*, 1952, **26**, 232.
[6] Clark and Hams, *Biochem. J.*, 1953, **55**, 839.

solution were then titrated with standard 0·1N-hydrochloric acid, phenolphthalein being used as indicator. Sampling was repeated at intervals. The difference between the blank and test solution titres was taken as a measure of the amount of 2,4-dichlorophenoxyacetic acid produced by hydrolysis of the amide.

Procedure 2. Bases too strong to permit direct titration. When strong bases, *e.g.* ammonia, ethanolamine, were products of the hydrolysis, direct titration of the excess of potassium hydroxide was not possible. The blank flask was omitted. Samples were taken at intervals from the test flask, chilled rapidly, and aliquot portions pipetted directly into an excess of *ca.* 0·5N-hydrochloric acid. The liberated 2,4-dichlorophenoxyacetic acid was extracted several times with ether, the combined ether solutions were washed until free from aqueous mineral acid, and evaporated, and the residue dissolved in aqueous alcohol and titrated with standard alkali.

Comparative runs on the same compound by both methods gave good agreement. At least two runs, in most cases three, were carried out on each compound. Samples were taken at intervals of 30 or 60 min., depending upon the rate of reaction. In the case of the isopropylamide (4) which was hydrolysed very slowly, samples were taken at intervals of 8 and 16 hr. alternately. 6—8 samples were taken during the course of each run.

The first-order rate constants and half-life periods obtained are shown in the Table.

DISCUSSION

Alkaline hydrolysis of amides is a bimolecular reaction [7,8] but under the conditions used, *i.e.*, a 5-molar excess of alkali, the kinetics of the reaction approximated very closely to first order. Plots of log[amide] against time did not deviate seriously from a straight line until at least 60% of the amide was hydrolysed. Since the principal aspect of the investigation, *i.e.*, relationship of chemical structure and stability to plant growth-regulating activity, was concerned only with the comparative stabilities of the compounds, this information was obtained in the form of half-life values calculated from the first-order rate constants.

Previous work on the alkaline hydrolysis rates of amides has been concerned with the effect of substituents in that portion of the molecule derived from the acid, and not, as in the present case, with varying substituents on the amide nitrogen. The mechanism of the reaction involves nucleophilic attack by a hydroxyl ion on the carbonyl carbon atom as the rate-determining step,[9] and the reaction will be accelerated by electron-withdrawing groups and retarded by electron-donating groups. The results now obtained show that this holds good for substituents on the amide nitrogen as well as those attached to the carbonyl carbon atom. The effect of donor groups is very noticeable in the case of methyl, ethyl, and isopropyl substituents. It could be argued that this effect is enhanced by steric retardation but when the very high hydrolysis rate of the disubstituted amides with bulky substituents, *e.g.* the diphenyl-amide, is taken into consideration this argument loses force. It appears, therefore, that the *N*-substituent is not sufficiently close to the site of reaction to have any marked steric effect.

There is no previous reference to comparison of hydrolysis rates of mono- and disubstituted amides, and it is noteworthy that the disubstituted amides are hydrolysed more rapidly than the corresponding monosubstituted amides. This is the case even though the substituents, taken individually, do not function as electron-withdrawing groups. No satisfactory explanation of this is offered.

[7] E. E. Reid, *Amer. Chem. J.*, 1899, **21**, 284, as quoted by Ingold.[9]
[8] Meloche and Laidler, *J. Amer. Chem. Soc.*, 1951, **73**, 1712.
[9] Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons, London, 1953, 784.