597. *The Alkaline Hydrolysis of Some* N-*Acyl-benzanilides and -benzamides, with a Note on the Behaviour of* N-*Acylbenzanilides in Sulphuric Acid.*

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Rate constants have been allotted for the competitive modes of alkaline hydrolysis of compounds $X{\cdot}C_6H_4{\cdot}CO{\cdot}NPh{\cdot}COPh$ and $X{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}COPh$, which result in the removal of $X{\cdot}C_6H_4{\cdot}CO$ or $Ph{\cdot}CO$. For *meta-* or *para-*substituents X, the rate of removal of $X{\cdot}C_6H_4{\cdot}CO$ can be correlated with the pK_a of the acid $X{\cdot}C_6H_4{\cdot}CO_2H$, or with the rate of hydrolysis of the amide $X{\cdot}C_6H_4{\cdot}CO{\cdot}NH_2$; to obtain the second correlation, the rates of hydrolysis of substituted benzamides have been measured. The rate of removal of $Ph{\cdot}CO$ varies, though to a smaller extent, with changes in X, and shows some relation to the strength of the acid $X{\cdot}C_6H_4{\cdot}CO_2H$. *ortho*-Substituents exert steric hindrance at the nearer carbonyl group, but influence the farther reaction centre in a more normal fashion.

Hydrolysis may be brought about rapidly by concentrated sulphuric acid, where a different mechanism operates, steric retardation disappears, and the weaker acid, rather than the stronger, is produced preferentially.

When two acyl groups are directly linked to a single central atom, they render each other mutually more susceptible to attack by nucleophilic reagents. Kinetic aspects of the behaviour of acid anhydrides[1] and of β-diketones[2] have been investigated, but only qualitative observations have hitherto been made on *NN*-diacylamines.[3]

TABLE 1. *Alkaline hydrolysis of the* N-*acylbenzanilides* R·CO·NPh·COPh *in methanol–water* (76 : 24, w/w) *at* 54·6°.

No.	Nature of R	Total rate of hydrolysis * (l. mole^{-1} min.$^{-1}$)	Percentage of Ph·CO_2H molecules formed at 54·6°	Percentage of Ph·CO_2H molecules formed at 71°	Rate of removal (l. mole^{-1} min.$^{-1}$) of R·CO	Rate of removal (l. mole^{-1} min.$^{-1}$) of Ph·CO
1	Phenyl	0·34			0·17	0·17
2	*o*-Nitrophenyl	0·30	100	96	nil	0·30
3	*m*-Nitrophenyl	4·3	13	12	3·7	0·6
4	*p*-Nitrophenyl	6·2	15	16	5·3	0·9
5	*o*-Bromophenyl	0·29	97	95	0·01	0·28
6	*m*-Bromophenyl	1·50	36	36	0·96	0·54
7	*p*-Bromophenyl	0·95	31	33	0·66	0·29
8	*o*-Tolyl	0·24		100	nil	0·24
9	*m*-Tolyl	0·25		54	0·11$_5$	0·13$_5$
10	*p*-Tolyl	0·23		59	0·09$_5$	0·13$_5$
11	*p*-Methoxyphenyl	0·21		61	0·08	0·13
12	*p*-t-Butylphenyl	0·22$_5$		77	0·05	0·17$_5$
13	α-Naphthyl	0·50		100	nil	0·50

* With respect to the anilide (initially *ca.* 0·01M) and potassium hydroxide (initially *ca.* 0·02M, or *ca.* 0·01M for the faster rates).

N-Benzoylbenzanilide is hydrolysed at least 1000 times faster than benzanilide; for *N*-benzoylbenzanilide (and similar compounds) it is therefore possible to follow the first stage of hydrolysis (Ph·CO·NPh·COPh + KOH ⟶ Ph·CO_2K + Ph·NH·COPh) without interference by subsequent similar reactions. In addition to *N*-benzoylbenzanilide itself, we have studied a series of unsymmetrical compounds X·C_6H_4·CO·NPh·COPh where X is *o*-, *m*-, or *p*-NO_2, *o*-, *m*-, or *p*-Br, *o*-, *m*-, or *p*-Me; *p*-OMe, or *p*-Bu^t, and the related α-naphthyl compound $C_{10}H_7$·CO·NPh·COPh. For all of these we have determined the (second-order) rate of alkaline hydrolysis, and, for the unsymmetrical compounds, also the relative rates of attack on the dissimilar carbonyl groups. This has been done in normal fashion by hydrolysis to completion, and quantitative analysis of either the acid (X·C_6H_4·CO_2H mixed with Ph·CO_2H) or the neutral products (X·C_6H_4·CO·NHPh mixed with Ph·CO·NHPh). By combining these observations we have obtained rate constants applicable to the competing, and concurrent, processes of hydrolysis, and our results are presented in Table 1.

TABLE 2. *Alkaline hydrolysis of the* N-*acylbenzamides* R·CO·NH·COPh *in methanol–water* (76 : 24, w/w) *at* 54·6°.

No.	R	Total rate of hydrolysis * (l. mole^{-1} min.$^{-1}$)	Percentage of Ph·CO_2H molecules formed	Rate of removal (l. mole^{-1} min.$^{-1}$) of R·CO	Rate of removal (l. mole^{-1} min.$^{-1}$) of Ph·CO
14	Phenyl	0·15		0·07$_5$	0·07$_5$
15	*p*-Nitrophenyl	20	25	15	5
16	*m*-Bromophenyl	2·5	35	1·6	0·9
17	α-Naphthyl	0·46	100 (at 71°)	nil	0·46

* With respect to the amide (initially *ca.* 0·01M) and potassium hydroxide (initially *ca.* 0·02M, or 0·01M for the faster rates).

We have similarly examined four *N*-acylbenzamides (X·C_6H_4·CO·NH·COPh; Table 2) (which are hydrolysed about 1000 times faster than the amides X·C_6H_4·CO·NH_2), and four unclassified *N*-acylanilides (Table 3).

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[1] *E.g.*, see bibliographies and collected data by Vles, *Rec. Trav. chim.*, 1933, **52**, 809; Gold, *Trans. Faraday Soc.*, 1948, **44**, 506; Berliner and Altschul, *J. Amer. Chem. Soc.*, 1952, **74**, 4110; Koskikallio, *Ann. Acad. Sci. Fennicae*, A II, 1954, **57**, 7; Tedder, *Chem. Rev.*, 1955, **55**, 805.

[2] Robinson and Bradley, *J.*, 1926, 2356; Kutz and Adkins, *J. Amer. Chem. Soc.*, 1930, **52**, 4036.

[3] Wheeler and Boltwood, *Amer. Chem. J.*, 1896, **18**, 381; Wheeler, *ibid.*, p. 695; Wheeler and Walden, *ibid.*, 1897, **19**, 129; Titherley and Stubbs, *J.*, 1914, **105**, 299.

TABLE 3. *Alkaline hydrolysis of unclassified* N-*acylanilides in methanol–water* (76 : 24, w/w) *at* 54·6°.

No.	Compound	Results
		[Rates (l. mole^{-1} min.$^{-1}$) with respect to the anilide (initially *ca.* 0·01M) and potassium hydroxide (initially *ca.* 0·01 or 0·02M)]
18	(Ph·CO)$_2$N·C$_6$H$_4$Br(*p*)	Total rate, 0·47; rate applicable to each Ph·CO group, 0·23$_5$
19	*p*-Br·C$_6$H$_4$·CO·N(COPh)·C$_6$H$_4$Br(*p*)	Total rate, 1·05; percentage of Ph·CO$_2$H molecules formed, 28; rate applicable to *p*-Br·C$_6$H$_4$·CO, 0·76; to Ph·CO, 0·29
20	(*m*-Br·C$_6$H$_4$·CO)$_2$NPh	Total rate, 2·8; rate applicable to each *m*-Br·C$_6$H$_4$·CO group, 1·4
21	(*p*-MeO·C$_6$H$_4$·CO)$_2$NPh	Total rate, 0·13; rate applicable to each MeO·C$_6$H$_4$·CO group, 0·06$_5$

TABLE 4. *Alkaline hydrolysis of benzamides* R·CO·NH$_2$ *in methanol–water* (78 : 22, w/w) *at* 54·6°.

No.	R	10^5k * (l. mole^{-1} min.$^{-1}$)	No.	R	10^5k * (l. mole^{-1} min.$^{-1}$)
22	Phenyl	33·6	29	*o*-Tolyl	1·8
23	*o*-Nitrophenyl	17·3	30	*m*-Tolyl	26·5
24	*m*-Nitrophenyl	360	31	*p*-Tolyl	19·4
25	*p*-Nitrophenyl	440	32	*p*-Methoxyphenyl	14·5
26	*o*-Bromophenyl	11·4	33	*p*-t-Butylphenyl	17·9
27	*m*-Bromophenyl	125	34	α-Naphthyl	5·0
28	*p*-Bromophenyl	95			

* With respect to the amide (initially *ca.* 0·08M) and potassium hydroxide (initially *ca.* 1·0M).

Alkaline hydrolysis of substituted benzamides has been studied by Reid[4] and by Meloche and Laidler.[5] In neither case were the conditions of solvent and temperature closely comparable with those which we found convenient for the study of the diacyl compounds; and our preliminary experiments, together with Kay's work[6] on the hydrolysis of *N*-benzoylbenzanilide, suggested that the corresponding benzanilides would be hydrolysed too slowly for convenient measurement.* We have therefore made the fresh measurements, on benzamides, which are set out in Table 4, and whose relation to the pK_a values of the corresponding acids is shown in line I of Fig. 1.

DISCUSSION

Inspection of Table 1 shows, first, that *ortho*-substituents almost completely prevent attack on the nearer reaction centre; and the steric hindrance appears to be more complete than in the case of the similarly substituted amides (Table 4).

For the *meta*- and *para*-substituted compounds the stronger acid is liberated preferentially; but the rate of hydrolysis of the invariant benzoyl group is not constant. Each acyl group greatly stimulates the hydrolysis of the other; and, superimposed upon this, variations in the nature of one acyl group alter, not only its own reactivity, but also the behaviour of the more distant reaction centre. In general, the more electron-attractive group stimulates the hydrolysis of the other acyl group without receiving, in return, an adequate compensation; and, in 7 cases of the 8 *meta*- or *para*-substituted compounds, the observed molecular ratio C$_6$H$_5$·CO$_2$H/X·C$_6$H$_4$·CO$_2$H is closer to unity than is suggested by an unsophisticated calculation from the rates of amide hydrolysis given in Table 4.

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* This conclusion was perhaps over-hasty. Asinger's results[7] suggest a rate of 11 × 10^{-4} l. mole^{-1} min.$^{-1}$ for the alkaline hydrolysis of benzanilide in aqueous methanol (MeOH–H$_2$O, 67 : 33, w/w) at 78° ± 2°. From this, benzanilide appears to be somewhat, but not very much, less easily hydrolysed than is benzamide.

[4] Reid, *Amer. Chem. J.*, 1899, **21**, 284; 1900, **24**, 397.

[5] Meloche and Laidler, *J. Amer. Chem. Soc.*, 1951, **73**, 1712.

[6] Kay, *Ber.*, 1893, **26**, 2853.

[7] Asinger, *J. prakt. Chem.*, 1935, **142**, 291.

Whilst the quantitative results of the hydrolysis of $X{\cdot}C_6H_4{\cdot}CO{\cdot}NPh{\cdot}COPh$ cannot be predicted simply from the rates of amide hydrolysis, we have found that, with the benzoyl group invariant, the rate of removal of *m*- or *p*-$X{\cdot}C_6H_4{\cdot}CO$ is directly related to the rate of hydrolysis of *m*- or *p*-$X{\cdot}C_6H_4{\cdot}CO{\cdot}NH_2$ (Fig. 2, line I), and, consequently, to the pK_a of the acid $X{\cdot}C_6H_4{\cdot}CO_2H$ (Fig. 1, line II). In these *meta*- and *para*-substituted compounds, the rate of hydrolysis of the invariant benzoyl group shows some degree of relationship (Fig. 1, line III) to the strength of the acids $X{\cdot}C_6H_4{\cdot}CO_2H$. The divergencies from line III are of the same order (15—20%) as those from line II; but the observations cover only an 8-fold range in rates in place of the 100-fold range covered by line II, and we hesitate to claim that they prove a quantitative relation.

FIG. 1.

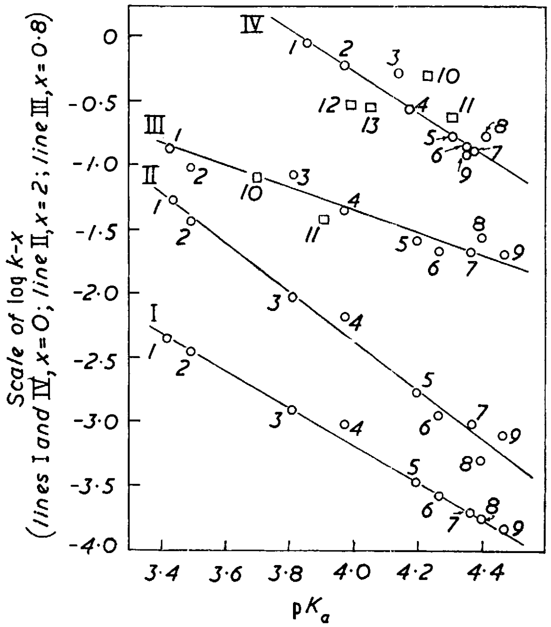

FIG. 2.

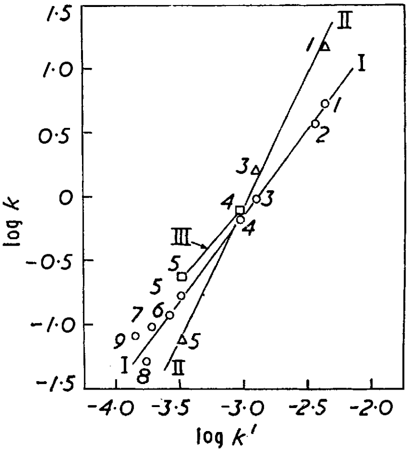

FIG. 1.

(I) Hydrolysis of $X{\cdot}C_6H_4{\cdot}CO{\cdot}NH_2$: plot of $\log k$ against pK_a of $X{\cdot}C_6H_4{\cdot}CO_2H$. Equation of line, $\log k = 2{\cdot}63 - 1{\cdot}45\text{p}K_a$.
(II) Removal of $X{\cdot}C_6H_4{\cdot}CO$ from $X{\cdot}C_6H_4{\cdot}CO{\cdot}NPh{\cdot}COPh$: plot of $\log k - 2$ against pK_a of $X{\cdot}C_6H_4{\cdot}CO_2H$. Equation of line, $\log k = 7{\cdot}24 - 1{\cdot}90\text{p}K_a$.
(III) Removal of Ph·CO from $X{\cdot}C_6H_4{\cdot}CO{\cdot}NPh{\cdot}COPh$: plot of $\log k - 0{\cdot}8$ against pK_a of $X{\cdot}C_6H_4{\cdot}CO_2H$. Equation of line, $\log k = 2{\cdot}94 - 0{\cdot}87\text{p}K_a$.
(IV) Removal of Ph·CO from $X{\cdot}C_6H_4{\cdot}CO{\cdot}NPh{\cdot}COPh$: plot of $\log k$ against pK_a of $X{\cdot}C_6H_4{\cdot}CH_2{\cdot}CO_2H$. Equation of line, $\log k = 6{\cdot}10 - 1{\cdot}59\text{p}K_a$.
In (III) and (IV) the points marked □ refer to *o*-substituted compounds, and have not been used in fixing the position of the lines.
Values of k are in l. mole^{-1} min.$^{-1}$.
Arabic numerals denote that X in $X{\cdot}C_6H_4$ is: 1, *p*-NO_2, 2, *m*-NO_2; 3, *m*-Br, 4, *p*-Br; 5, H; 6, *m*-Me; 7, *p*-Me; 8, *p*-Bu^t; 9, *p*-OMe; 10, $X{\cdot}C_6H_4$ replaced by α-$C_{10}H_7$; 11, *o*-Me; 12, *o*-NO_2; 13, *o*-Br.

FIG. 2.

Logarithms of rates of removal (k, l. mole^{-1} min.$^{-1}$) of groups $X{\cdot}C_6H_4{\cdot}CO$ against logarithms of rates of alkaline hydrolysis (k', l. mole^{-1} min.$^{-1}$) of amides $X{\cdot}C_6H_4{\cdot}CO{\cdot}NH_2$. All determinations in MeOH–H_2O (76 : 24 for k; 78 : 22 for k', w/w) at 54·6°.
(I) From molecules $X{\cdot}C_6H_4{\cdot}CO{\cdot}NPh{\cdot}COPh$. Points ○.
(II) From molecules $X{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}COPh$. Points △.
(III) From molecules $X{\cdot}C_6H_4{\cdot}CO{\cdot}N(COPh){\cdot}C_6H_4Br(p)$. Two points □ only.
For arabic numericals see Fig. 1.

Consideration of the geometry of the molecules led us to compare the rate of hydrolysis of the invariant benzoyl group with the strength of the phenylacetic acids $X{\cdot}C_6H_4{\cdot}CH_2{\cdot}CO_2H$. It is certain that, in $X{\cdot}C_6H_4{\cdot}CO{\cdot}NPh{\cdot}COPh$, the three benzene rings cannot be co-planar. If complete conjugation does not extend from one acyl group to the other, then the transmission of any effect from the variant acyl group to the benzoyl reaction centre might well resemble the transmission to the carboxyl group in phenylacetic acids, rather than in benzoic acids. This relation is shown in line IV of Fig. 1; but comparison of the " fit " of the experimental points to lines III and IV provides no evidence in favour of a change from the pK_a values of the benzoic to those of the phenylacetic acids.

For the *ortho*-substituted compounds the rate of hydrolysis at the more distant carbonyl group might well be consistent with the rough relations (Fig. 1, lines III and IV) found for the *meta*- and *para*-compounds. Of the four points available for comparison with line III, two fit well, but two cannot be plotted in the area of the figure. Points from all four *ortho*-substituted compounds can at least be plotted against line IV; but the agreement is reasonable only in one case.

Comparison of the *N*-acylbenzamides (Table 2) with the corresponding *N*-acylbenzanilides shows that the removal of the phenyl group may either decrease (compare 14 with 1) or increase (compare 15 with 4) the rate of hydrolysis; but caution in comparison is desirable, since the *N*-acylbenzamides contain a slightly acidic hydrogen atom. For example, *N*-benzoylbenzamide dissolves, though slowly, in an excess of cold 0·02M-sodium hydroxide; and it is reprecipitated unchanged by hydrochloric acid, by carbon dioxide, or by addition of ammonium acetate sufficient to give a pH of *ca.* 8·8. If salt formation were complete in methanolic alkali at 54·6°, then the concentration of hydroxyl ions would be reduced, and the pseudo-unimolecular reaction

$$[(C_6H_5{\cdot}CO)_2N]^- + H_2O \longrightarrow (C_6H_5{\cdot}CO_2)^- + C_6H_5{\cdot}CO{\cdot}NH_2$$

would take place. We were, however, able to follow the course of hydrolysis by back-titration with standard hydrochloric acid; and the constants we obtained showed no noticeable " drift." But these constants (Table 2) should be accepted only for what they experimentally are—values calculated on the basis of the second-order rate formula, and on the assumption that, in methanol–water (76 : 24, w/w) at 55°, the *N*-acylbenzamides do not effectively reduce the concentration of hydroxyl ions by salt formation.

The results collected in Tables 2 and 3 do, however, suggest that relations, similar to, but not identical with, those already discussed for the series $X{\cdot}C_6H_4{\cdot}CO{\cdot}NPh{\cdot}COPh$, could be established for the variants $X{\cdot}C_6H_4{\cdot}CO{\cdot}NR'{\cdot}COPh$. For $R' = H$ (Table 2), the three points available for the rate of removal of $X{\cdot}C_6H_4{\cdot}CO$ are approximately linear (Fig. 2, line II), with a steeper slope than for line I (for which $R' = Ph$). Excluding the α-naphthamide (17), three points are available for the rate of removal of Ph·CO; plotted as for Fig. 1 (lines III and IV), they suggest a similar degree of relationship, with a better linear " fit " by use of the benzoic acids as reference compounds. All that can be said, with confidence, is that any linear relations would be steeper than lines III and IV. For example, compare ratios for the rate of removal of Ph·CO: Table 1, No. 4/No. 1 = 5·3; Table 2, No. 15/No. 14 = 67. In general it thus appears that the *N*-acylbenzamides show a greater variation in rates of hydrolysis than do the *N*-acylbenzanilides; we think this may be due to the greater possibility of planarity when the third benzene ring is absent.

Two points, from *p*-bromoanilides (Table 3), are also indicated in Fig. 2. They, and the corresponding rates of elimination of Ph·CO, are consonant with our other observations.

The Behaviour of N-*Acylbenzanilides in Sulphuric Acid.*—*N*-Benzoylbenzanilide reacts with concentrated sulphuric acid at room temperature and, on dilution with water (added as ice), hydrolysis to a mixture of benzanilide and benzoic acid is found to have occurred. It was our intention to examine the initial stage (in sulphuric acid) of this reaction kinetically, but the reaction was too rapid for us to follow, and seemed almost concurrent with the process of dissolution. We were, however, able to determine the relative rates of attack on the two acyl groups, in compounds of the type $X{\cdot}C_6H_4{\cdot}CO{\cdot}NPh{\cdot}COPh$.

Conditions were found in which the diacyl compounds reacted to completion, but the resultant anilides were unaffected. Our results, based on analyses of the anilide or acid fractions, are given in Table 5.

TABLE 5. *Hydrolysis of the* N-*acylbenzanilides*, $X·C_6H_4·CO·NPh·COPh$, *by means of sulphuric acid* (98%, w/w; *at room temperature*) *and subsequent dilution with water.*

X	*o*-NO_2	*m*-NO_2	*p*-NO_2	*o*-Br	*m*-Br	*p*-Br	*o*-Me	*m*-Me	*p*-Me
$C_6H_5·CO_2H$ (molar %)	89	99	100	60	97	87	10	44	20

It can be generally concluded that the acid hydrolysis is of a totally different character from the alkaline. For *meta*- and *para*-substituted compounds, the weaker acid is now eliminated preferentially. The *ortho*-substituted compounds show no sign of steric retardation; in fact, the reverse is true since, for constant X, the group $X·C_6H_5·CO$ is eliminated most readily ($\equiv$ lowest $Ph·CO_2H$) when X is in the *ortho*-position. These results appear to be explicable in terms of the production of acylium ions (*e.g.*, $Ph·CO·NPh·COPh + H^+ \longrightarrow Ph·CO^+ + Ph·NH·COPh$): compare the behaviour of methyl mesitoate,[8] and the mechanism proposed by Duffy and Leisten [9] for the hydrolysis of amides in sulphuric acid.

EXPERIMENTAL

Reaction rates were evaluated on the basis of natural logarithms, and the temperature was controlled within 0·1°.

Rate of Hydrolysis of the Diacyl Compounds.—The acyl-anilide or -amide (0·8—1·0 mmole) was weighed into a two-necked flask (115 ml., B.14 ground-glass sockets), and dissolved in neutral methanol (80 ml.). The flask was then heated in the thermostat under a reflux condenser with a carbon dioxide guard-tube, and with the second socket stoppered. After 15 min., standard potassium hydroxide (20 ml.; *ca.* 0·1M; pre-heated in the same thermostat) was added. Samples (10 ml.) were run into ice-cold neutral methanol, and titrated with standard hydrochloric acid (*ca.* 0·01M), with α-naphtholphthalein as indicator. In the determination of some of the fast rates (*e.g.*, $p-NO_2·C_6H_4·CO·NPh·COPh$) it was preferable to halve the concentration of the potassium hydroxide. These conditions correspond to a methanol–water ratio of 76·3 : 23·7 w/w, and a volume of 102·5 ml. at 54·6°; the molarities of the reagents have been adjusted to this basis in the calculation of the reaction rates.

It was found that the reaction did not run smoothly from the moment of addition of the alkali. There appeared to be an undue extent of hydrolysis at the time of mixture; and better results, without " drift " of the constant, were obtained by taking the time of the first sample (5—10 min. after mixture) as the initial point of the run. The alkali concentration at this new zero time was obtained directly by titration of the sample, whilst the concentration of the diacyl compound was calculated from the original weight and the quantity of alkali which had already been absorbed.

Rate of Hydrolysis of the Benzamides.—The amide (*ca.* 4 mmoles) was weighed into a 50 ml. graduated flask, and dissolved in methanol (*ca.* 25 ml.). Standard potassium hydroxide (10 ml.; *ca.* 5M) was added, with cooling in ice, and the volume made up (now at room temperature) to 50 ml. with methanol. Samples (4 ml.) were sealed in alkali-resistant " boron-free " glass tubes,* and heated in the thermostat.

These conditions correspond to a methanol : water ratio of 77·8 : 22·2, w/w, and a volume of 51·6 ml. at 54·6°. The reaction rates given in Table 4 are the true rates in terms of molarities at 54·6°.

The samples were analysed by washing the well-cooled contents of the tube into a semimicro-Kjeldahl distillation apparatus, which already contained magnesium chloride solution (5 ml.; 2N) to neutralise the potassium hydroxide. The ammonia was distilled, in steam, from the

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* In the use of " boron-free " glass we have followed the example of Meloche and Laidler.[5] We were supplied with the following analysis: Al_2O_3, 2·5; B_2O_3, 0·78; CaO, 5·4; MgO, 3·6; K_2O, 0·35; SiO_2, 70·0; Na_2O, 17·8; SO_3, 0·2%.

[8] Treffers and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 1708; Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953, p. 771.

[9] Duffy and Leisten, *Nature*, 1956, **178**, 1242; *J.*, 1960, 545.

suspension of magnesium hydroxide into standard hydrochloric acid (25 ml. of *ca.* 0·01M), and the ammonia determined by back-titration with potassium hydroxide, Methyl Red being used as indicator.

Complete Alkaline Hydrolysis of One Acyl Group from the Diacyl Compounds, and Separation of Neutral from Acidic Products.—The *N*-acylanilide (1 mmole) was heated with methanol (8 ml.) and aqueous potassium hydroxide (2 ml. of 3·5M) under reflux on a steam-bath for 30 min. (temperature of boiling liquid, 71°). The methanolic solution and methanolic rinsings were then transferred to a constant-extraction apparatus, mixed with distilled water (50 ml.), and extracted with ether for 2 hr. to obtain the anilide hydrolysis products. After acidification with concentrated hydrochloric acid (1 ml.), the acid hydrolysis products were extracted (3 hr.) with fresh ether. The anilide and acid mixtures were isolated and dried by evaporation, followed by the addition and subsequent boiling off of dry acetone (3 × 50 ml. in each case), and finally by heating for 10 min. in an oven at 100°. Other methods of separation were tried, but discarded; for example, simple drying in an oven caused losses in weight, which could be avoided by the azeotropic removal of water in acetone. We standardised our procedure on synthetic mixtures of benzanilide, anisanilide, benzoic acid, and anisic acid; we were able to recover over 99% of the anilide material, and over 98% of the acid material.

" Complete hydrolyses " at 54·6° were carried out in the same manner, but with heating for 40 hr. in the thermostat. There was no significant difference between the analytical results obtained after hydrolysis at 71° and at 54·6°. We therefore consider that, when " complete hydrolysis " at 54·6° was inconveniently slow, the proportions determined after hydrolysis at 71° can be used without undue error.

The *N*-acylamides (15, 16, 17) were treated in similar fashion.

Complete Hydrolysis of One Acyl Group from the Diacyl Compounds by Means of Concentrated Sulphuric Acid, and Separation of Neutral from Acidic Products.—The *N*-acylanilide (1 mmole) was dissolved in sulphuric acid (2 ml. of 98% w/w), and set aside at room temperature for 16 hr. Ice (25 g.) was then added and, after melting, the aqueous mixture was extracted with methylene dichloride (2 × 30 ml.). The combined extracts were washed with water (3 × 15 ml.), the solvent was evaporated on a steam-bath, and the residue dissolved in methanol (2 ml.). The methanolic solution was neutralised (to phenolphthalein) with dilute aqueous potassium hydroxide, and the mixture thereafter treated by the technique described previously. Separate tests indicated that the anilide products were not significantly hydrolysed under these conditions.

Analysis of the Products of " Complete Hydrolysis."—In general, this was done by elemental analysis of the anilide mixtures. The accuracy of the analysis, expressed as the molecular percentage of BzOH obtained from Ar·CO·NPh·Bz, depends not only on the complete isolation of the anilide fraction, and the accuracy of the elemental analysis, but also on the difference between the theoretical analyses for Ar·CO·NHPh and Bz·NHPh. An element of judgment is involved: we have laid most weight on the carbon analyses. Thermal analysis by m. p. determination has been used when elemental analysis could not be expected to be satisfactory. We consider that the reported percentages of benzoic acid are accurate to one or two units of %. To give an indication of the degree of accuracy which can be obtained, we report in full our findings for one typical compound.

Two hydrolyses of *N*-*m*-bromobenzoylbenzanilide were carried out at 71°, and the anilide fractions isolated. These gave C, 69·0 and 69·2% (BzOH, 37 and 36%); H, 4·8 and 4·5% (BzOH, 34 and 48%); Br, 12·9 and 12·4% (BzOH, 36 and 35%); thermal analysis gave m. p.s of 140·8° and 140° (BzOH, 34 and 35%); estimated best value for molar percentage of BzOH, 36. Two hydrolyses were carried out at 54·6°, and the anilide fractions isolated. These gave C, 69·5 and 69·0% (BzOH, 35 and 37%); H, 4·6 and 4·8% (BzOH, 44 and 34%); estimated best value for molar percentage of BzOH, 36. Two hydrolyses were carried out by means of sulphuric acid at 20°, and the anilide fractions isolated. These gave C, 57·4 and 56·3% (BzOH, 95 and 100 + %: analysis of 56·5% C = 100%); H, 4·2 and 4·0% (BzOH, 65 and 77%); estimated best value for molar percentage of BzOH, 97%. Similar procedures were used in the remaining 15 cases.

Preparation of Materials.—*General.* The requisite aromatic acids were prepared by standard methods, or purchased. Acid chlorides were prepared from the acids by means of thionyl chloride, and were used as sources of compounds of the general formulæ Ar·CO·NH$_2$, Ar·CO·NHPh, (Ar·CO)$_2$NPh; and, from benzamidine hydrochloride, of the acylbenzamidines

Ph·C(:NH)·NH·COAr. The unsymmetrical *N*-acylanilides were prepared by the action of the sodium salt of the appropriate acid on the imidoyl chloride (generally Ph·N:CClPh, from benzanilide; *e.g.*, Ph·N:CClPh + Ar·CO$_2$Na ⟶ Ar·CO·NPh·COPh + NaCl [10,11]); and the *N*-acylbenzamides were prepared by hydrolysis of the (crude) acylbenzamidines. Unless specifically mentioned, the physical properties of known compounds were in satisfactory agreement with those recorded in the literature.

Phenylacetic acids. The three acids, which were required for measurement of their dissociation constants, were obtained by the route Ar·CH$_3$ ⟶ Ar·CH$_2$Br ⟶ Ar·CH$_2$·CN ⟶ Ar·CH$_2$·CO$_2$H. The cyanides were prepared in general accordance with methods which have been described,[12] and were hydrolysed essentially as described [13] by Hill and Short. They were purified by boiling, whilst in the form of sodium salts, with charcoal in water, and by repeated crystallisation from ligroin (b. p. 60—80°); *o*-tolylacetic acid, plates, m. p. 89° (lit.,[13-15] 87—90°) (Found: C, 72·0; H, 6·7. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%); *m*-tolylacetic acid, plates, m. p. 64° (lit.,[14] 61°) (Found: C, 71·8; H, 6·8%); and *m*-bromophenylacetic acid, plates, m. p. 101° (lit.,[16,17] 97—103°) (Found: C, 44·8; H, 3·2. Calc. for $C_8H_7BrO_2$: C, 44·7; H, 3·3%). Dr. S. R. C. Hughes [18] reports provisional values of $10^5K_{\text{th.}}$ (25°): *o*-tolylacetic acid, 4·936 ± 0·017 (pK = 4·31); *m*-tolylacetic acid, 4·334 ± 0·009 (pK = 4·36); and *m*-bromophenylacetic acid, 7·252 ± 0·014 (pK = 4·14). Details of the method of measuring the dissociation constants will be published elsewhere.

Anilides and symmetrical N-*acylanilides.* In general the amine was dissolved in pyridine (0·1 mole in 50 ml.), and the acid chloride (0·06—0·09 mole for anilides, 0·25—0·3 mole for *N*-acylanilides) added portionwise, with efficient cooling. After being warmed for 4—5 hr. at 80—90°, the mixture was poured into cold 2N-hydrochloric acid (450 ml.), and the precipitate crystallised from ethyl acetate (for anilides) or ethanol (for *N*-acylanilides). The following merit description: *m*-bromobenzanilide, needles, m. p. 142° (lit.,[19] 137°) (Found: C, 55·9; H, 3·8; N, 5·1; Br, 29·2. Calc. for $C_{13}H_{10}BrNO$: C, 56·5; H, 3·6; N, 5·1; Br, 29·0%); N-*benzoylbenzo*-p-*nitroanilide*, pale yellow needles, m. p. 205° (Found: C, 68·9; H, 4·6. $C_{20}H_{14}N_2O_4$ requires C, 69·4; H, 4·1%); N-*benzoylbenzo*-p-*bromoanilide*, plates, m. p. 179° (Found: C, 63·1; H, 4·0; N, 3·3; Br, 21·3. $C_{20}H_{14}BrNO_2$ requires C, 63·2; H, 3·7; N, 3·6; Br, 21·0%); N-m-*bromobenzoyl*-m-*bromobenzanilide*, plates, m. p. 160° (Found: C, 52·9; H, 3·1; N, 3·2. $C_{20}H_{13}Br_2NO_2$ requires C, 52·3; H, 2·9; N, 3·1%).

N-*Anisoylanisanilide.* We were unable to prepare this compound from aniline or anisanilide with anisoyl chloride in pyridine, or by the action of sodium anisate on phenyl *p*-methoxybenzimidochloridate. It was subsequently made by the action of anisoyl chloride on ethyl *N*-phenyl-*p*-methoxybenzimidate [MeO·C$_6$H$_4$·C(OEt):NPh]. Anisanilide (5·8 g.) and phosphorus pentachloride (5·1 g.) were fused together until evolution of hydrogen chloride ceased, and phosphorus oxychloride was removed by warming *in vacuo*. The solid residue was taken up in ligroin (*ca.* 100 ml., b. p. 40—60°), and filtered from insoluble material; the filtrate was cooled in ice and treated with a solution of sodium (1 g.) in ethanol (25 ml.). After removal of the precipitated sodium chloride in water, the ligroin layer was dried and the ligroin removed *in vacuo* to leave the crude ethyl imidoate. This was warmed for 17 hr. at 120—130° with anisoyl chloride (2 g.); the product was shaken with ether and water, and the ether layer yielded N-*anisoylanisanilide* on evaporation: this formed needles, m. p. 139°, from ethanol (Found: C, 73·0; H, 5·4; N, 4·2. $C_{22}H_{19}NO_4$ requires C, 73·1; H, 5·3; N, 3·9%).

Imidoyl chlorides. These were made in normal fashion by heating the anilide with phosphorus pentachloride, and subsequently distilling *in vacuo*.

Benzo-*p*-bromophenylimidoyl chloride (b. p. 160°/20 mm.) appears to be new, and was characterised as the cyanide: the imidoyl chloride (3 g.) was dissolved in dry ether (100 ml.), traces of

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[10] Mumm, *Ber.*, 1910, **43**, 886.

[11] Mumm, Hesse, and Volquartz, *Ber.*, 1915, **48**, 379.

[12] Atkinson and Thorpe, *J.*, 1907, **91**, 1687; Titley, *J.*, 1926, 508.

[13] Hill and Short, *J.*, 1935, 1123.

[14] Radziszewski and Wispek, *Ber.*, 1885, **18**, 1279.

[15] Best and Thorpe, *J.*, 1909, **95**, 261; Clemo and Swan, *J.*, 1946, 617; Julian, Karpel, Magnani, and Meyer, *J. Amer. Chem. Soc.*, 1948, **70**, 180.

[16] Campbell and McKail, *J.*, 1948, 1251.

[17] Jackson and White, *Jahresber.*, 1880, 482; Gabriel, *Ber.*, 1882, **15**, 834; Mauthner, *J. prakt. Chem.*, 1917, **95**, 62.

[18] Dr. S. R. C. Hughes, personal communication.

[19] Kottenhahn, *Annalen*, 1891, **264**, 170.

insoluble anilide were removed, and the filtrate was shaken for 20 hr. with potassium cyanide (10 g. in 100 ml. of water). The ether layer was dried ($CaCl_2$) and evaporated *in vacuo*: the residue yielded yellow needles (m. p. 118°) of *benzo*-p-*bromophenylimidoyl cyanide* (Found: C, 58·7; H, 3·5; N, 9·3. $C_{14}H_9BrN_2$ requires C, 58·9; H, 3·1; N, 9·8%) on crystallisation from ligroin.

Unsymmetrical N-*acylanilides.* These were prepared by the method of Mumm,[11,10] who, however, gives few practical details. We shook the acid (0·1 mole) with sodium hydroxide (0·095 mole) in water (100—200 ml.) until the solution gave a neutral reaction with universal indicator paper. The undissolved acid was collected, and the filtrate shaken for 20 hr. with a solution of the required imidoyl chloride (0·03 mole; usually 6·5 g. of benzophenylimidoyl chloride) in dry ether (50 ml.). If insoluble, the resultant *N*-acylanilide was collected, washed with water, and crystallised from ethanol. If it was soluble, the mixture was shaken with chloroform (200 ml.), and the chloroform–ether layer separated, dried (Na_2SO_4), and evaporated to yield an oil. This was dissolved in the minimum of boiling ethanol, filtered whilst hot, and set aside to cool, yielding crystals of the *N*-acylanilide. The following were sparingly soluble in ethanol, insoluble in benzene, chloroform, ether, and ligroin: N-o-*nitrobenzoylbenzanilide*, pale yellow needles, m. p. 165° (Found: C, 69·6; H, 4·0; N, 8·2. $C_{20}H_{14}N_2O_4$ requires C, 69·4; H, 4·1; N, 8·1%); N-p-*nitrobenzoylbenzanilide*, faintly yellow needles, m. p. 176° (Found: C, 69·4; H, 4·1; N, 8·1%); and N-p-*nitrobenzoylbenzo*-p-*nitroanilide*, pale yellow plates, m. p. 197° (Found: C, 61·5; H, 3·4; N, 10·3. $C_{20}H_{13}N_3O_6$ requires C, 61·3; H, 3·3; N, 10·7%). N-α-*Naphthoylbenzanilide* formed needles, m. p. 197°, sparingly soluble in ethanol, insoluble in ether and ligroin, but easily soluble in benzene and chloroform (Found: C, 81·7; H, 5·2; N, 4·2. $C_{24}H_{17}NO_2$ requires C, 82·0; H, 4·9; N, 4·0%). The following were soluble in benzene, chloroform, ethanol, and ether, but sparingly soluble in ligroin: N-o-*bromobenzoylbenzanilide*, prisms, m. p. 137° (Found: C, 62·8; H, 3·6; N, 4·4. $C_{20}H_{14}BrNO_2$ requires C, 63·2; H, 3·7; N, 3·6%), and N-m-*bromobenzoylbenzanilide*, prisms, m. p. 141° (Found: C, 63·0; H, 3·7; N, 3·8%). N-m-*Toluoylbenzanilide* formed needles, m. p. 157°, soluble in chloroform and ether, sparingly soluble in ethanol and ligroin (Found: C, 80·0; H, 5·7. $C_{21}H_{17}NO_2$ requires C, 80·0; H, 5·4%). N-p-*t-Butylbenzoylbenzanilide* formed needles, m. p. 142°, soluble in benzene, chloroform, and ether, insoluble in methanol (Found: C, 80·3; H, 6·8. $C_{24}H_{23}NO_2$ requires C, 80·7; H, 6·4%). N-p-*Bromobenzoylbenzo*-p-*bromoanilide* formed needles, m. p. 128°, soluble in benzene, chloroform, ethanol, and ether (Found: C, 52·5; H, 3·2; N, 3·3. $C_{20}H_{13}Br_2NO_2$ requires C, 52·3; H, 2·9; N, 3·1%). Other unsymmetrical *N*-acylanilides (Nos. 3, 7, 8, 10, and 11 of Table 1) have already been described.[11,20]

N-*Acylamides.* A modification of Titherley's method [21] gave an improved yield (77%) of *N*-benzoylbenzamide. Benzoyl chloride (18 g.) was added portionwise to a well-cooled solution of benzamide (20 g.) in pyridine (100 ml.), the mixture heated for 3 hr. at 50°, cooled, and poured into water (350 ml.), and the precipitated *N*-benzoylbenzamide crystallised from ethanol.

Unsymmetrical *N*-acylamides were prepared in 55—70% yield by Lossen and Neubert's method.[22] Benzamidine hydrochloride (0·03 mole) was shaken with the required acid chloride (0·01 mole) for 20 hr. in the presence of saturated potassium carbonate solution (70 ml.), a little chloroform (8 ml.), and ethanol (2 ml.). The chloroform layer was separated, washed with water, dried, and combined with a second (similarly treated, but larger; 100 ml.) chloroform extract. Evaporation yielded the crude *N*-acylbenzamidine, which could be hydrolysed directly to the *N*-acylbenzamide, or purified by crystallisation from chloroform–ligroin: N-o-*nitrobenzoylbenzamide*, yellow plates, m. p. 120° (Found: C, 62·2; H, 4·0. $C_{14}H_{11}N_3O_3$ requires C, 62·4; H, 4·1%); N-p-*nitrobenzoylbenzamidine*, yellow rods, m. p. 145° (Found: C, 62·4; H, 3·6%); N-m-*bromobenzoylbenzamidine*, needles, m. p. 110° (Found: C, 55·7; H, 3·9; Br, 26·7. $C_{14}H_{11}BrN_2O$ requires C, 55·4; H, 3·7; Br, 26·4%); and N-α-*naphthoylbenzamidine*, needles, m. p. 93° (Found: C, 78·8; H, 5·5; N, 10·2. $C_{18}H_{14}N_2O$ requires C, 78·8; H, 5·1; N, 10·2%). Hydrolysis of the *N*-acylbenzamidines (0·01 mole) was achieved by heating them for 4 hr. at 50° with hydrochloric acid (80 ml. of 0·2M). The precipitate of *N*-acylamide was collected, washed with water, and crystallised from aqueous methanol: N-o-*nitrobenzoylbenzamide*, yellow needles, m. p. 160° (Found: C, 62·2; H, 3·7; N, 10·0. $C_{14}H_{10}N_2O_4$ requires C, 62·2; H,

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[20] Wheeler and Johnson, *Amer. Chem. J.*, 1903, **30**, 24; Freundler, *Compt. rend.*, 1903, **137**, 712.

[21] Titherley, *J.*, 1904, **85**, 1673.

[22] Lossen and Neubert, *Annalen*, 1891, **265**, 148.

3·7; N, 10·4%); N-p-*nitrobenzoylbenzamide*, yellow needles, m. p. 174° (Found: C, 61·8; H, 3·7%); N-m-*bromobenzoylbenzamide*, needles, m. p. 111° (Found: C, 55·3; H, 3·5; N, 4·9. $C_{14}H_{10}BrNO_2$ requires C, 55·3; H, 3·3; N, 4·6%); and N-α-*naphthoylbenzamide*, needles, m. p. 165° (Found: C, 78·7; H, 5·0; N, 5·0. $C_{18}H_{13}NO_2$ requires C, 78·5; H, 4·7; N, 5·1%).

Attempts to prepare *N*-*p*-bromobenzoyl- and *N*-*p*-nitrobenzoyl-benzamidine by the method [$Ph{\cdot}C({:}NH){\cdot}NH_2 + Ar{\cdot}CO_2Ph \longrightarrow Ph{\cdot}C({:}NH){\cdot}NH{\cdot}COAr + PhOH$] of Titherley and Stubbs[3] were unsatisfactory: although some of the *N*-acyl compound was obtained, the main product was the benzamidine salt. These were identified by analysis, and comparison with materials produced by an orthodox route: *benzamidine* p-*nitrobenzoate*, prisms, m. p. 278° (Found: C, 58·7; H, 4·7; N, 14·4. $C_{14}H_{13}N_3O_4$ requires C, 58·5; H, 4·6; N, 14·6%); *benzamidine* m-*bromobenzoate*, prisms, m. p. 250° (Found: C, 51·8; H, 4·3; Br, 24·9. $C_{14}H_{13}BrN_2O_2$ requires C, 52·3; H, 4·1; Br, 24·9%); and *benzamidine* p-*bromobenzoate*, plates, m. p. 255° (Found: C, 52·5; H, 4·0; Br, 25·0%).

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