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STUDIES IN HETEROCYCLIC CHEMISTRY—II

THE FORMATION OF BENZIMIDAZOLES BY THE ACTION OF ALKALI ON ACYLATED *o*-PHENYLENE DIAMINES

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Abstract—The alkaline hydrolysis of diacylated *o*-phenylenediamines proceeds by a two stage process giving initially *o*-amidoanilines and then benzimidazoles. Although the reaction is not accelerated participation by the neighbouring amino group is probable in the ring closure reaction; conversely there is no evidence for participation by the neighbouring amido group in the initial hydrolysis stage. The IR spectra of the monoacyl *o*-phenylenediamines show they are correctly represented as *o*-amidoanilines rather than 2-hydroxybenzimidazolines.

The most convenient route to 2-substituted benzimidazoles lies in the action of acylating agents on *o*-phenylenediamines. Under the appropriate conditions benzimidazoles are formed directly; alternatively the N,N′-diacyl compounds can be obtained and, as with the corresponding benzothiazoles and benzoxazoles, the products of their partial hydrolysis subsequently converted to the heterocyclic system. In Part I of this series[1] it was shown that the alkaline hydrolysis of N,S-diacyl *o*-aminothiophenols is facilitated achimerically by the amide group. A study has now been made of the alkaline hydrolysis of N,N′-diacyl *o*-phenylenediamines to explore the possibility that a similar process might also occur in this system.

Two criteria for the recognition of neighbouring group participation were available for the hydrolysis of N,S-diacyl *o*-aminothiophenols: the rate of S-acyl fission was markedly accelerated by the *o*-amide system; and the reaction was accompanied by S → N acyl migration. The second criterion is not available for the study of the hydrolysis of N,N′-diacyl *o*-phenylenediamines and consequently no attempt was made to examine the hydrolysis of mixed diacyl derivatives. However, *o*-amidoanilines formed by the loss of one acyl group are—unlike *o*-amidothiophenols—stable compounds which can be isolated. To simplify the analysis of the reaction of the diacyl compounds, the influence of alkali on the mono-acyl derivatives was examined first.

(1) *Monoacyl* o-*phenylenediamines.* Preliminary studies showed that at room temperature *o*-amidoanilines were largely unaffected by dilute alkali but at 50° their decomposition proceeded at a measurable rate. There appear to be two possible competing processes for the decomposition of the mono-amide *viz* direct ring closure and elimination of water giving the benzimidazole, and simple hydrolysis to *o*-phenylenediamine. The UV spectrum of the reaction mixture indicated that the former mechanism predominated and that benzimidazole was the principal product; this was confirmed by the isolation of 2-propylbenzimidazole in 85% yield from the action of alkali on *o*-butyramidoaniline. Despite these observations the similarity of the rates of hydrolysis of the corresponding anilides to those of the *o*-amidoanilines under the same conditions suggested that some simple hydrolysis might also occur. Careful

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[1] A. J. Collings and K. J. Morgan, *Tetrahedron* **20**, 2167 (1964).

examination of the residue from the action of alkali on *o*-butyramidoaniline revealed the presence of a small amount of a second hydrolysis product which was identified as *o*-phenylenediamine by its IR spectrum. Previous attempts to detect this product using TLC had not been successful but quantitative examination showed that the sensitivity of this method was low for *o*-phenylenediamine: with synthetic mixtures similar to the crude reaction product the limit of detectability represented a yield of ca. 10%.

The rate of formation of benzimidazoles from acylaminoanilines was studied kinetically using an excess of 0·2 N NaOH at 50°. The results gave good first order plots and the observed *pseudo* first order rate constants, together with those for the anilides are shown in Table 1. The course of the reaction was followed spectrometrically by observing the appearance of absorption due to the benzimidazole: the families of spectra so obtained showed good isobestic points. Through the simultaneous formation of a small amount of *o*-phenylenediamine the kinetic measurements are subject to a systematic error, which leads to a high value for the apparent rate constant. The similarity of the absorption characteristics of *o*-phenylenediamine to those of the other compounds present in the solution precludes any attempt to correct specifically for this effect, however, it is readily shown that in the present system the resultant error in rate constant will not be greater than 10% corresponding to the formation of 10% *o*-phenylenediamine.*

TABLE 1. ACTION OF ALKALI ON SOME AROMATIC AMIDES

	Pseudo first order rate constants (0·2 N NaOH at 50°)		
Acyl group	Diacyl phenylenediamines (sec^{-1})	Monoacyl phenylenediamines (sec^{-1})	Anilides (sec^{-1})
o-CH_3CO—	15×10^{-6}	$4{\cdot}2 \times 10^{-6}$	$8{\cdot}8 \times 10^{-6}$
o-C_2H_5CO—	$7{\cdot}2 \times 10^{-6}$	$5{\cdot}0 \times 10^{-6}$	$5{\cdot}8 \times 10^{-6}$
o-C_3H_7CO—	$2{\cdot}6 \times 10^{-6}$	$2{\cdot}2 \times 10^{-6}$	$2{\cdot}4 \times 10^{-6}$
m-CH_3CO—	18×10^{-6}	$9{\cdot}0 \times 10^{-6}$	

It is clear that these results do not indicate any overall acceleration in the rate of reaction of the amide accompanying the introduction of an *o*-amino group. However it is probable[2] than in the absence of some participitation the donor action of the *o*-amino group would cause a reduction in the rates for the amidoanilines to values significantly below those for the anilides. Further the almost exclusive formation of benzimidazole requires that the amino group participate in the reaction, for under these conditions *o*-phenylenediamine is not susceptible to attack by carboxylate ion. The ability to compete successfully with the normal hydrolytic process of attack by hydroxyl ion on the amide carbonyl group indicates that nucleophilic attack by the amino group can provide the mechanism for participitation. It is unlikely that this in

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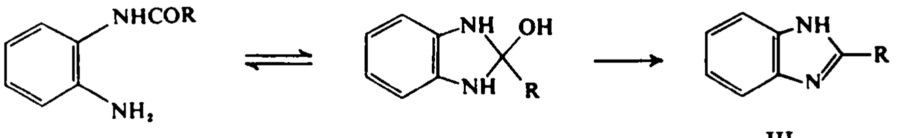
[*] Blank experiments with solutions of *o*-phenylenediamine indicated that under the reaction conditions a small amount of decomposition occurred. This reaction, which was reproducible, led to the production of traces of a coloured substance showing absorption at 273 and 325 mμ. A similar coloration was noted in the kinetic reaction mixtures. The effect of the formation of this on the kinetic measurements is to reduce the value of the observed rate constant and consequently to reduce the apparent error due to the formation of *o*-phenylenediamine.

[2] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* pp. 758, 759. Bell, London (1953).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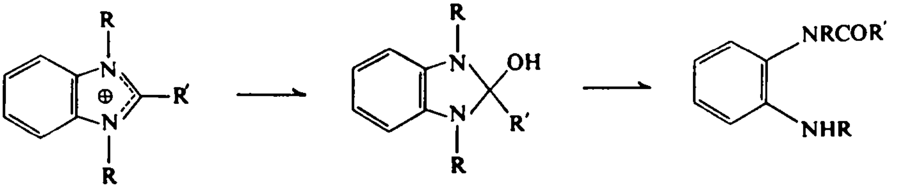
IV V VI

itself is the rate determining step for equilibration of *o*-amidoaniline and 2-hydroxybenzimidazoline (II) will not require the presence of alkali. Consequently it is probable that the essential base catalysed reaction in the formation of benzimidazole is the elimination of water from the intermediate 2-hydroxybenzimidazoline (II) by a route analogous to that found in the formation of Schiff's bases.[3] Support for this is provided by the properties of 1,3 dialkylbenzimidazolium salts (IV). Under alkaline conditions they are converted to carbinol bases, which have been assigned similar structures (V) to the 2-hydroxybenzimidazolines postulated as intermediates in the ring closure reaction. With the carbinol bases there can be no elimination to give benzimidazoles and the alternative facile equilibration of the carbinol bases gives N-acyl-N,N′-dialkyl-*o*-phenylenediamines (VI) as the products of the reaction.

It is of interest to contrast the behaviour of the *o*-acylaminoanilines with that of the *o*-acylaminothiophenols. The latter are stable under alkaline conditions and undergo elimination to benzothiazoles only in the presence of acids;[1] the difference in the two reactions is clearly ascribable to the greater stability of the anion formed by the thiophenol.

The IR spectra of *o*-amidoanilines were recorded for solutions in methylene chloride (Table 2). Both in the amino and carbonyl stretching regions the bands

TABLE 2. BANDS IN THE IR SPECTRA OF SOME AROMATIC AMIDES*

	Frequency (cm^{-1})					
	Diacyl phenylenediamines		Monoacyl phenylenediamines		Anilides	
Acyl group	N—H	C=O	N—H	C=O	N—H	C=O
o-CH_3CO—	3416	1683	3416	1684	3432	1694
o-C_2H_5CO—	3414	1679	3416	1681	3430	1692
o-C_3H_7CO—	3414	1679	3417	1681	3431	1691
m-CH_3CO—	3431	1695	3432	1692		
p-CH_3CO—	3300† 3170†	1665†	3433	1684		

* solution in CH_2Cl_2. † nujol mull.

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[3] A. V. Willi, *Helv. Chim. Acta* **39**, 1193 (1956); B. Kastening, L. Holleck and G. A. Melkonian, *Z. Elektrochem.* **60**, 130 (1956); W. P. Jencks, *J. Amer. Chem. Soc.* **81**, 475 (1959); E. H. Cordes and W. P. Jencks, *Ibid.* **84**, 832 (1962); K. Koehler, W. Sandstrom and E. H. Cordes, *Ibid.* **86**, 2413 (1964).

appear as a number of incompletely resolved multiplets: in each case the band centre is well defined and it is these frequencies that are quoted. The IR spectra clearly show that these compounds are correctly represented as amides (I) rather than as 2-hydroxybenzimidazolines (II). The IR spectra[4] of the corresponding N,N′-dialkyl derivatives (VI) show that they too have the amide structure rather than that of the cyclic carbinol bases. A clear distinction is apparent in the spectra between the amino and carbonyl frequencies of the *o*-acylaminoanilines and the anilides. The low frequencies found for both bands in the spectra of the former indicate the occurrence of intramolecular hydrogen bonding in these compounds representing an alternative mode of interaction to the amino-carbonyl interaction necessary for ring closure. The low carbonyl frequency and normal amino frequency shown by *p*-acetamidoaniline reflects the mesomeric interaction of the amino group; no significant displacements of frequency are apparent in the spectrum of the *meta* isomer.

(2) *Diacyl* o-*phenylenediamines.* For the hydrolysis of the diacyl derivatives there appeared to be three feasible routes *viz.* stepwise hydrolysis of the acyl groups giving first the monoacyl compound and then *o*-phenylenediamine; hydrolysis to monoacyl compound followed by elimination of water giving benzimidazole as the final product; and cyclization to a 1-acyl-2-hydroxybenzimidazoline (VII) leading to benzimidazole by hydrolysis and elimination. From the results of the hydrolysis it was apparent that the formation of *o*-phenylenediamine was likely to be of minor importance and in agreement with this none of the compound was detected by TLC. However, following the earlier observation of the low sensitivity of this means of detecting it careful examination of the final hydrolysis products from *o*-diacetamidobenzene and *o*-dibutyramidobenzene was made. In both cases a small amount of material (ca. 10%) was obtained which was shown by IR and TLC to be largely *o*-phenylenediamine.

Differentiation between the second and third routes of hydrolysis followed from the time taken for benzimidazole to appear among the products. Both TLC and UV spectroscopy showed that the sole detectable product of the initial stages of the reaction was the monoacyl compound and only in the later stages did benzimidazole become a significant product.* Ultimately a good recovery of benzimidazole is possible: after 10 days a solution of *o*-dibutyramidobenzene in 1·5 N alkali at 60° gave 2-propylbenzimidazole (86%). While this evidence does not exclude the possibility of a slow hydroylsis of the diacyl compound giving some benzimidazole directly, it strongly suggests that the major part of the reaction proceeds by initial hydrolysis to monoacyl compound.† Further, since the hydrolysis of a 1-acyl-2-hydroxybenzimidazoline can be expected to be facile and since the resultant 2-hydroxybenzimidazoline (II) has already been shown to exist preferentially as *o*-acylaminoaniline, this route offers

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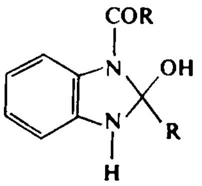
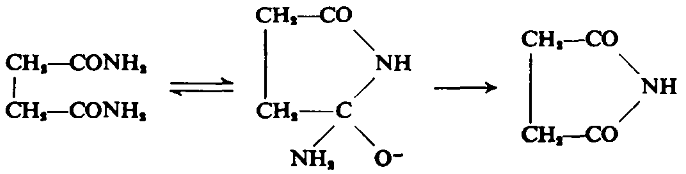
* The detection of both *o*-acylaminoanilines and benzimidazoles by thin layer chromatography is considerably more sensitive than it is for the diamine. Detection of benzimidazoles by their characteristic UV spectra provides an additional particularly sensitive method for their location.

† Quantitative evidence for this mechanism is provided by evaluation of rate constants for the subsequent decomposition of the monoacyl derivatives from the data obtained for the diacyl compounds. The accuracy of these values is limited by the small amount of benzimidazole formed under the reaction conditions during the normal hydrolysis period of the diacyl compounds. Nevertheless, the results ($k_2 \times 10^4$ sec^{-1} acetyl, 9·0; propionyl, 6·5; butyryl, 2·5) are in satisfactory agreement with those determined directly.

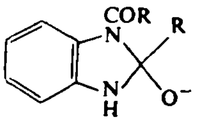
[4] C. W. Smith and R. S. Rasmussen, *J. Amer. Chem. Soc.* **71**, 1082 (1949).



VII



VIII IX X



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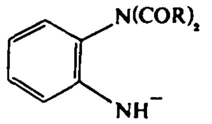
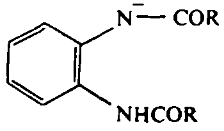


XII



XIII

merely a possible mechanism for an anchimerically assisted hydroylsis of di- to monoacyl compound.

The rates of hydrolysis of the diacyl compounds were similar to those of the monoacyl derivatives and they were conveniently studied under *pseudo* first order conditions in 0·2 N NaOH at 50°. In all cases the reactions gave good first order rate plots for the rate of formation of monacyl compound; values of the rate constants are given in Table 1.

The observed rates are close to those shown under the same conditions by the *m*-substituted isomer and by the anilides and indicate no acceleration in the rate of hydrolysis accompanying the introduction of an *ortho* amide group. The failure to observe an acceleration cannot in this instance be attributed to electron release by the amide group for this has a sigma value of zero[5] but some retardation may arise from the steric effect of the *ortho* substituent.[2]

The apparent absence of anchimeric assistance is in marked contrast with the usual effects of a neighbouring amide group on such a reaction. Thus the presence of an adjacent amide group is reflected in greatly increased rates of alkaline hydrolysis for diacyl *o*-aminothiophenols,[1] for phthalamide[6] and for succinamide[7] (VIII). In the hydrolysis of these three types of compound a similar mechanism has been attributed to the interaction of the amide group. Loss of a proton allows nucleophilic attack by the amide on the adjacent carboxyl function (IX) and this is followed by fission of the adduct to give the N,N-diacyl derivative (X). In the case of succinamide and phthalamide the resultant cyclic imides are sufficiently stable to be isolated.

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[5] D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).

[6] J. A. Shafer and H. Morawetz, *U.S. Dept. Comm. Office Tech. Serv.* A.D. 273, 645, 11 (1962); J. A. Shafer and H. Morwetz, *J. Org. Chem.* **28**, 1899 (1963); P. Crooy and A. Bruylants, *Bull. Soc. Chim. Belg.* **73**, 44 (1964); A. Bruylants and F. de Kemmeter, *Ibid.* **73**, 637 (1964).

[7] F. Kezdy and A. Bruylants, *Bull. Soc. Chim. Belg.* **68**, 225 (1959); B. Vigneron, P. Crooy, F. Kezdy and A. Bruylants, *Ibid.* **69**, 616 (1960).

Application of a similar scheme to the diacyl *o*-phenylenediamines would lead to an intermediate (XI) adduct which could collapse in two ways: to a rearranged N,N-diacyl anion (XII) or to regenerate N,N-′diacyl anion (XIII). The former would correspond to the process found for the other amides but in this instance it differs in that the leaving group is neither lost irreversibly from the molecule nor possessed of high thermodynamic stability. In this system the best and most stable leaving group is the amide anion (XIII) and its loss regenerates starting material. Consequently although the neighbouring amide group may well interact with the reaction centre, it is unable to participate in the hydrolysis reaction. It seemed possible that if the adduct persisted long enough to allow protonation on the nitrogen atom the alternative mode of collapse might be stabilized but studies of the rate of hydrolysis in less alkaline solutions showed no acceleration relative to that of simple anilides. In view of these results there is no reason to believe that this reaction proceeds by a mechanism other than that of normal amide hydrolysis.

TABLE 3. UV SPECTRA* OF SOME AROMATIC AMIDES

	λ_{max} (mμ)	ε_{max}	λ_{max} (mμ)	ε_{max}	λ_{max} (mμ)	ε_{max}	λ_{max} (mμ)	ε_{max}
Diacylamino benzenes, $C_6H_4(NHCOR)_2$								
o-$NHCOCH_3$	[239]	$1·3 \times 10^4$						
m-$NHCOCH_3$	234	$3·05 \times 10^4$			[280·5]	$1·3 \times 10^3$	292	$1·1 \times 10^3$
p-$NHCOCH_3$			264	$2·2 \times 10^4$				
o-$NHCOC_2H_5$	[240]	$1·25 \times 10^4$						
o-$NHCOC_3H_7$	[240]	$1·25 \times 10^4$						
Monoacylamino anilines, $C_6H_4NH_2(NHCOR)$								
o-$NHCOCH_3$	[234]	$8·7 \times 10^3$					291	$2·95 \times 10^3$
m-$NHCOCH_3$	[246·5]	$1·2 \times 10^4$					295·5	$2·5 \times 10^3$
o-$NHCOC_2H_5$	[234]	$8·6 \times 10^3$					291	$3·0 \times 10^3$
o-$NHCOC_3H_7$	[234]	$9·0 \times 10^3$					291	$3·05 \times 10^3$
Anilides, C_6H_5NHCOR								
$NHCOCH_3$	241	$1·4 \times 10^4$			[279]	$4·5 \times 10^2$		
$NHCOC_2H_5$	242	$1·5 \times 10^4$			[279]	$5·0 \times 10^2$		
$NHCOC_3H_7$	242	$1·5 \times 10^4$			[279]	$5·0 \times 10^2$		
Benzimidazoles								
2-CH_3	242·5	$6·0 \times 10^3$	[270]	$4·8 \times 10^3$	273	$6·4 \times 10^3$	279·5	$7·3 \times 10^3$
2-C_2H_5	243	$6·2 \times 10^3$	[270·5]	$5·3 \times 10^3$	274	$7·1 \times 10^3$	280	$8·1 \times 10^3$
2-C_3H_7	243	$6·4 \times 10^3$	[270·5]	$5·5 \times 10^3$	274	$7·4 \times 10^3$	280	$8·4 \times 10^3$

* Solution in MeOH

EXPERIMENTAL

Preparation of N,N′*-diacyl* o*-phenylenediamines.* The diamine was treated with a small excess of the appropriate carboxylic anhydride and the mixture warmed for a few min. After cooling the mixture was poured into water and the crude diamide collected and recrystallized. The following compounds were prepared in this way: N,N′-diacetyl-*o*-phenylenediamine, m.p. 186° (from water); N,N′-diacetyl-*m*-phenylenediamine, m.p. 188° (from water); N,N′-diacetyl-*p*-phenylenediamine, m.p. 163° (from acetic acid); N,N′*-dipropionyl-*o*-phenylenediamine*, m.p. 136° from aq. MeOH. (Found: C, 65·4; H, 7·2; N, 12·4. $C_{12}H_{16}N_2O_2$ requires: C, 65·4; H, 7·3; N, 12·7%); N,N′*-dibutyryl-*o*-phenylenediamine*, m.p. 132° from aq. MeOH. (Found: C, 67·9; H, 7·9; N, 11·3. $C_{14}H_{20}N_2O_2$ requires: C, 67·7; H, 8·1; N, 11·3%.)

Preparation of monoacyl o*-phenylenediamines.*[8] A mixture of finely ground *o*-nitroacetanilide (18 g) and 90 mesh Fe filings (11 g) was added during 3 min to a hot solution of acetic acid (5 ml) in

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[8] M. A. Phillips, *J. Chem. Soc.* 174 (1928).

water (100 ml) containing a few drops of butanol to reduce foaming. The mixture was boiled for 5 min and then cooled. After adjusting the pH to 9 by the addition of NaOH the solution was filtered and evaporated giving a solid residue. The solid was purified by chromatography over silica gel with ethyl acetate–acetone as eluent giving *o*-acetamidoaniline, m.p. 132° (from benzene).

Similarly prepared were o-*propionamidoaniline*, m.p. 122° from benzene. (Found: C, 66·1; H, 7·3; N, 17·0. $C_9H_{12}N_2O$ requires: C, 65·8; H, 7·4; N, 17·1%) and o-*butyramidoaniline*, m.p. 131° from benzene. (Found: C, 67·4; H, 8·0, N, 15·4. $C_{10}H_{14}N_2O$ requires: C, 67·4; H, 7·9; N, 15·7%.)

Preparation of benzimidazoles.[9] A mixture of *o*-phenylenediamine (1 mole) and carboxylic acid (1 mole) was boiled under reflux with 4 N HCl. The mixture was allowed to cool, poured into water and the solution made neutral. The benzimidazole was collected and recrystallized. The following compounds were prepared in this way: 2-methylbenzimidazole, m.p. 175° (from water); 2-ethylbenzimidazole, m.p. 173° (from water); 2-propylbenzimidazole, m.p. 157° (from water).

Products formed by the action of alkali on acylated o-*phenylenediamines*

(a) o-*Acetamidoaniline.* A mixture of N,N′-diacetyl-*o*-phenylenediamine (10·6 g) and NaOH (2·2 g) in MeOH (150 ml) was boiled under reflux for 10 hr. The solvent was removed *in vacuo* and the residue extracted into benzene giving *o*-acetamidoaniline, m.p. 132°. TLC indicated the presence of a small amount of starting material in the crude product.

(b) 2-*Methylbenzimidazole.* N,N′-diacetyl-*o*-phenylenediamine (1·457 g) in 0·2 N methanolic NaOH (190 ml) was boiled under reflux for 5 weeks. The solution was neutralized, evaporated to dryness and the residue crystallized from water (20 ml) giving 2-methylbenzimidazole (0·69 g, 69%) m.p. 173–175°. The solubility of 2-methylbenzimidazole (100 mg/20 ml) suggests that at least a further 10% remains in solution.

Ether extraction of the mother liquor gave a solid mixture (150 mg) containing *o*-phenylenediamine, and 2-methylbenzimidazole (TLC).

(c) 2-*Propylbenzimidazole.* (i) A solution of *o*-di-butyramidobenzene (1·354 g) in 0·2 N methanolic NaOH (190 ml) was boiled under reflux for two weeks. TLC showed the main product to be *o*-butyramidoaniline but also revealed the presence of *o*-phenylenediamine, 2-propylbenzimidazole and starting material. (ii) A mixture of dibutyramidobenzene (1·516 g) and NaOH (1·5 g) in MeOH (25 ml) was boiled under reflux for 10 days. At the end of this time MeOH was evaporated *in vacuo* and the residue treated with water. The solution was neutralized (pH 7·6) with HCl and evaporated. Recrystallization of the residue from water (40 ml) gave 2-propylbenzimidazole (0·86 g, 86%), m.p. 156–157°. The solubility of 2-propylbenzimidazole in water indicates that a further quantity (40 mg, 4%) remains in solution. Ether extraction of the mother liquor gave a gum (76 mg) containing largely *o*-phenylenediamine (IR) contaminated with 2-propylbenzimidazole (TLC). (iii) A mixture of *o*-butyramidoaniline (1·379 g) and NaOH (1·5 g) in MeOH (25 ml) was boiled under reflux for 10 days. The product was isolated in the usual way and recrystallization from water (40 ml) gave 2-propylbenzimidazole (1·06 g, 85%), m.p. 156–157°. Extraction of the mother liquor with ether (3 × 50 ml) gave a solid residue (86 mg, 10%) whose IR spectrum and thin layer chromatogram showed it to be mainly *o*-phenylenediamine.

Rate measurements. Solutions of the amides and NaOH were separately thermostatted at 50°. At the start of a reaction, NaOH (5 ml) was added to amide solution (100 ml) giving a concentration of alkali 0·2 N and amide 0·003–0·02 M. Aliquots (5 ml) were withdrawn at suitable intervals and the reaction frozen by dilution. The resultant solutions were examined spectroscopically. All rate constants are the mean of at least two experiments.

Thin-layer chromatography. Plates were coated with silica gel (Camag D5 orDS5). A mixture of AcOEt (80%) and acetone (20%) was used to develop the chromatograms and spots were detected with the aid of a UV lamp. The limit of reliable detection of *o*-phenylenediamine was found to be 3 gpl in the presence of other hydrolysis fractions.

Spectroscopic measurements. UV spectra were measured on a Unicam SP 800; IR measurements were made with a Perkin–Elmer 237 spectrometer fitted with a read-out accessory. IR spectra were calibrated against indene (NH) and water vapour (CO).

Acknowledgement—One of us (A. M. T.) thanks S.R.C. for a maintenance grant.

[9] M. A. Phillips, *J. Chem. Soc.* 2395 (1928).