841. *Intramolecular Reactions of Amides. Part V.*[1] *Polar Effects on the Nucleophilicity of Amido-groups*

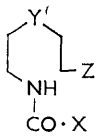
By A. CHAMBERS and C. J. M. STIRLING

The products obtained from *N*-acyl-*N'*-toluene-*p*-sulphonyl-*N'*-2-iodoethylethylenediamines (I; Y = NTs, Z = I) on treatment with ethanolic sodium ethoxide have been investigated with respect to change in the structure of the acylamino-group. Electron-withdrawal by the group X favours formation of cyclic product.

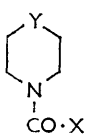
A rectilinear relationship is found between the rate of cyclisation and σ^* for the group X; this indicates that only polar effects upon cyclisation are important. The implications of the small but positive value of ρ^* for the reaction are discussed.

σ^* for the phenylthiomethyl group has been determined.

IN Part III,[2] the behaviour of a series of amides of general structure (I) on treatment with ethanolic sodium ethoxide was reported. It was observed that in compounds (I; X = Ph; Z = Cl, I, or OTs) an increase in the inductive withdrawal of electrons by the group Y caused an increase in the extent of cyclisation [to give product (II)] as opposed to elimination [to give the olefin (III)] and external substitution [to give the ethoxy-compound (I; Z = OEt)]. It was suggested that an increase in the inductive effect of Y increased the acidity of the benzamido-group and hence its ability to function as an " internal " nucleophile, causing cyclisation.



(I)



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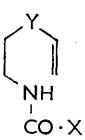
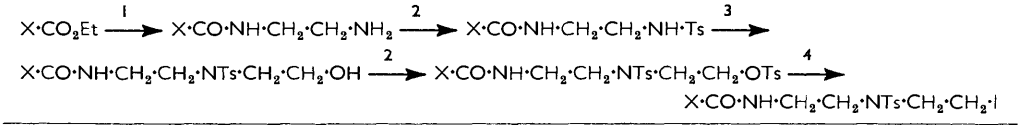


(III)

This Paper is concerned with a quantitative investigation of the effect of change in the group X upon the rate of cyclisation of the amides (I). Two of the variables whose alteration was studied in Part III have been kept constant. Group Y has been made toluene-*p*-sulphonamido, because a negligible amount of external substitution occurs in compounds of this type [1,2] and the reaction products are thereby simplified. Iodides (Z = I) have been used throughout as they are readily obtainable and react at convenient rates.

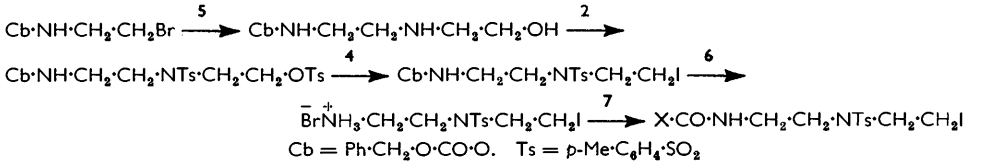
Preparation of Materials.—The routes used to obtain the iodides are outlined in Schemes 1 and 2. The latter was preferred because of its more general applicability.

Scheme 1



[1] Part IV, A. Chambers and C. J. M. Stirling, preceding Paper.
[2] C. J. M. Stirling, *J.*, 1962, 3676.

Scheme 2



Cb = Ph·CH_2·O·CO·O. Ts = p-Me·C_6H_4·SO_2

Reagents: 1, NH_2·CH_2·CH_2·NH_2; 2, TsCl–pyridine; 3, NaOH–ClCH_2·CH_2·OH; 4, NaI–EtOH; 5, NH_2·CH_2·CH_2·OH; 6, HBr–AcOH; 7, X·CO·Cl–Na_2CO_3

The iodides obtained by these routes are listed in Table 1.

TABLE 1

Amides X·CO·NH·CH_2·CH_2·NTs·CH_2·CH_2I (IV)

X	M. p.	Recryst. from	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
Bu^t	61—62°	Pet.–Et_2O	79	43·1	5·6	6·6	$C_{16}H_{25}IN_2O_3S$	42·5	5·6	6·2
Et	93—95	EtOH	78	40·0	5·2	6·5	$C_{14}H_{21}IN_2O_3S$	39·6	5·0	6·6
Me †	120—121	EtOH	96	38·2	4·9	—	$C_{13}H_{19}IN_2O_3S$	38·05	4·7	—
m-MeO·C_6H_4	121—122	EtOH	46	45·85	4·8	—	$C_{19}H_{23}IN_2O_4S$	45·4	4·6	—
p-Cl·C_6H_4	149—150	MeOH	79	42·8	4·1	5·2	$C_{18}H_{20}ClIN_2O_3S$	42·7	4·0	5·5
Ph·S·CH_2	84—85	EtOH	86	44·4	5·3	5·8	$C_{19}H_{23}IN_2O_3S_2$	44·0	4·5	5·4
Ph·SO_2·CH_2 ‡	159—160	MeOH	34	41·1	4·1	5·2	$C_{19}H_{23}IN_2O_5S_2$	41·5	4·2	5·1

* Light petroleum, b. p. 80—100°. † Anhydride used. ‡ Also obtained by oxidation of the thio-derivative.

EXPERIMENTAL

For general directions see Part III.[2] Dry ethanol was obtained by the magnesium–iodine method. Ethyl phenylthioacetate (b. p. 82°/0·1 mm., n_D^{22} 1·5445) was obtained from ethyl bromoacetate and sodium thiophenoxide in ethanol (lit.,[3] b. p. 144—145°/14 mm.). Ethyl phenylsulphonylacetate was obtained from the reaction of sodium benzenesulphinate with ethyl bromoacetate in ethanol.[4] It had m. p. 43·5—44° (from benzene–light petroleum). Phenylthio- and phenylsulphonyl-acetyl chlorides were obtained by the methods of Uyeda[5] and Otto,[6] respectively. Authentic specimens of *N*-acyl-*N'*-toluene-*p*-sulphonylethylenediamines (Table 2) were obtained by the Schotten–Baumann method from *N*-toluene-*p*-sulphonylethylenediamine.[7]

N-p-*Anisoylethylenediamine Hydrochloride*.[8]—Ethyl *p*-anisate (67 g.) and sodium-dried ethylenediamine (190 ml.) were kept (sealed tube) at 140° for 36 hr. Ethanol and the excess of ethylenediamine were removed under reduced pressure and the residue was taken up in ethanol. NN'-*Di*-p-*anisoylethylenediamine* (5·3 g.) was filtered off, m. p. 232° (from ethanol) (Found: C, 65·4; H, 6·1. $C_{18}H_{20}N_2O_4$ requires C, 65·8; H, 6·1%). The filtrate was saturated with hydrogen chloride, yielding a precipitate of the *hydrochloride* (60%), m. p. 209° (from ethanol–water) (Found: C, 51·8; H, 6·5. $C_{10}H_{15}ClN_2O_2$ requires C, 52·1; H, 6·55%).

The *m*-anisoyl analogue was obtained as an oil in *ca.* 70% yield.

N-p-*Anisoyl*-N'-*toluene*-p-*sulphonylethylenediamine*.—The preceding hydrochloride (52 g.) was treated successively with an excess of aqueous 0·7N-sodium hydroxide and toluene-*p*-sulphonyl chloride (80 g.) in acetone (100 ml.). The mixture was shaken for 20 min., acidified, and extracted with dichloromethane. The extracts were evaporated and the residue was dissolved in aqueous 2N-sodium hydroxide. The filtered solution was acidified and re-extracted with dichloromethane. Evaporation of the extracts gave the sulphonamide (54%), m. p. 118° (from ethanol) (Found: C, 58·8; H, 5·7. $C_{17}H_{20}N_2O_4S$ requires C, 58·6; H, 5·8%).

The *m*-anisoyl analogue was obtained in a similar way. Details are given in Table 2.

N-p-*Anisoyl*-N'-2-*hydroxyethyl*-N'-*toluene*-p-*sulphonylethylenediamine*.—2-Chloroethanol (37

[3] R. Pummerer, *Ber.*, 1910, **43**, 1401.
[4] Cf. A. Michael and A. M. Comey, *Amer. Chem. J.*, 1883, **5**, 116.
[5] Y. Uyeda, *J. Chem. Soc., Japan*, 1931, **52**, 410.
[6] R. Otto, *J. prakt. Chem.*, 1889, **148**, 505.
[7] D. H. Peacock and U. C. Dutta, *J.*, 1934, 1303.
[8] Cf. A. J. Hill and S. R. Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 822.

g., 4 mol.) was added dropwise with stirring to the preceding amide (40 g.) in aqueous 2N-sodium hydroxide (2·5 mol.) at 100°. When addition was complete, the mixture was kept at 100° for 45 min. and subsequently cooled, made alkaline, and extracted with dichloromethane. Evaporation of the extracts and treatment of the residue with light petroleum gave the *amido-alcohol* (78%), m. p. 101° (from ethanol (Found: C, 58·25; H, 5·9. $C_{19}H_{24}N_2O_5S_2$ requires C, 58·1; H, 6·2%).

The m-*anisoyl analogue* (66%), m. p. 87° (from ethanol), was obtained in a similar way (Found: C, 58·1; H, 6·2%).

N-p-*Anisoyl*-N-2-*iodoethyl*-N′-*toluene*-p-*sulphonylethylenediamine*.—Toluene-*p*-sulphonyl chloride (17 g.) was added to the preceding alcohol (24 g.) in pyridine (39 ml.) at −5°. The mixture was kept at 0° for 2 hr. Water was added slowly, and the mixture was subsequently extracted with chloroform. The extracts were washed with 2N-hydrochloric acid and evaporated. The oily toluene-*p*-sulphonate (*m*-anisoyl analogue also liquid) was refluxed with sodium iodide (54 g.) in ethanol (180 ml.) for 30 hr. The mixture was diluted with water and extracted with chloroform. The extracts were washed with aqueous sodium thiosulphate and evaporation gave the *iodide* (67%), m. p. 116—119° (from benzene) (Found: C, 45·35; H, 4·6. $C_{19}H_{23}IN_2O_4S$ requires C, 45·4; H, 4·6%).

Details of the *m*-anisoyl analogue are given in Table 1.

N-*Benzyloxycarbonyl*-N′-2-*hydroxyethylethylenediamine*.—2-Benzyloxycarbonylaminoethyl bromide [9] (4 g.) was kept with 2-aminoethanol (7 g., 7·5 mol.) at 95° for 40 min. A slight excess of aqueous sodium hydroxide was added and the mixture was extracted with dichloromethane. Evaporation of the extracts gave the *hydroxy-amide* (85%), m. p. 56—57° (from benzene–light petroleum) (Found: C, 60·3; H, 7·4. $C_{12}H_{18}N_2O_3$ requires C, 60·5; H, 7·6%).

N-*Benzyloxycarbonyl*-N′-*toluene*-p-*sulphonyl*-N′-2-*toluene*-p-*sulphonyloxyethylethylenediamine*.—Toluene-*p*-sulphonyl chloride (51 g., 2·5 mol.) was added slowly to the preceding hydroxy-amide (25·5 g.) in collidine (125 ml.) at 0°. The mixture was kept at 0° for 2 hr. and subsequently at 20° for 16 hr. Water was added and extraction was with chloroform. The extracts, after being washed successively with ice-cold 2N-hydrochloric acid and saturated aqueous sodium hydrogen carbonate, were evaporated yielding the *amido-ester* (42·6 g.), m. p. 70—71° (from ethanol) (Found: C, 57·4; H, 5·4. $C_{26}H_{30}N_2O_7S_2$ requires C, 57·1; H, 5·5%).

N-*Benzyloxycarbonyl*-N′-2-*iodoethyl*-N′-*toluene*-p-*sulphonylethylenediamine*.—The preceding ester (10 g.) and sodium iodide (13·7 g., 5 mol.) were refluxed in ethanol (80 ml.) for 6 hr. The mixture was diluted with water and the chloroform extracts, after being washed with aqueous sodium thiosulphate, gave the *iodide* (9·07 g.), m. p. 101—102° (from ethanol) (Found: C, 45·5; H, 4·7. $C_{19}H_{23}IN_2O_4S$ requires, C, 45·4; H, 4·6%). A metastable form of m. p. 91° was sometimes obtained.

N-2-*Iodoethyl*-N-*toluene*-p-*sulphonylethylenediamine Hydrobromide*.—The preceding iodide (5·05 g.) was treated with 50% w/v hydrogen bromide in acetic acid (10 ml.), and when evolution of carbon dioxide had ceased the mixture was diluted with anhydrous ether. The precipitated *hydrobromide* (95%) had m. p. 173—174° (from ethanol) (Found: C, 29·7; H, 4·2; N, 6·4. $C_{11}H_{18}BrIN_2O_2S$ requires C, 29·4; H, 4·0; N, 6·2%).

General Procedure for the Preparation of N-*Acyl*-N′-2-*iodoethyl*-N′-*toluene*-p-*sulphonylethylenediamines*.—The preceding salt (0·002 mole) in water (10 ml.) together with the acid chloride (0·004 mole) in dichloromethane (10 ml.) was treated with sodium hydroxide (1 mol.) and sodium carbonate (2 mol.) in water (6 ml.). The mixture was shaken vigorously, and after reaction was complete it was extracted with dichloromethane. Evaporation yielded the amido-iodide which in some cases was contaminated with amido-bromide. The latter was converted into the former by refluxing the crude product with ethanolic sodium iodide as above. Details of amido-iodides obtained by this procedure are given in Table 1.

Reactions of Amido-iodides with Ethanolic Sodium Ethoxide. General Procedure.—Equal volumes of a 0·1M-solution of the iodide and of 2N-sodium ethoxide in ethanol at 78° were mixed and kept at 78° for the times given in Table 5. The mixture was then added to saturated brine (3 vol.) and brought to pH 3 with hydrochloric acid. The mixture was set aside for 48 hr. and extracted with chloroform, the extracts being washed with saturated aqueous sodium hydrogen carbonate. Evaporation of the extracts gave a residue, which was chromatographed on alumina

[9] E. Katchalski and D. Ben-Ishai, *J. Org. Chem.*, 1950, **15**, 1067.

in benzene solution. Elution with the same solvent gave the products (Table 5), which were identified by mixed melting points and by comparison of their infrared spectra with those of authentic specimens. Acidification of the alkaline washings gave the free carboxylic acid produced by cleavage of the acylamino-group. This acid is derived [2] very largely from the piperazine produced in the reaction, and corrected yields of piperazine obtained have been included in Table 5.

N-*Acyl*-N'-*toluene*-p-*sulphonylpiperazines*.—*N*-toluene-*p*-sulphonylpiperazine was obtained only in poor yield by the literature method.[10] The following method was consequently employed. *N*-2-Iodoethyl-*N*-toluene-*p*-sulphonylethylenediamine hydrobromide was warmed with a slight excess of aqueous 2N-sodium hydroxide. The solid which separated was extracted

TABLE 2

Reference compounds

X·CO·NH·CH_2·CH_2·NHTs (V) X·CO·N⟨ ⟩N·Ts (VI)

Compound	M. p.	Recryst. from	Found (%) C	H	N	Formula	Required (%) C	H	N
(V; X = Me) *	109°	EtOH	51·3	6·4	—	$C_{11}H_{16}N_2O_3S$	51·5	6·3	—
(V; X = Et)	83—85	PhH–Pet †	53·1	6·5	10·2	$C_{12}H_{18}N_2O_3S$	53·3	6·7	10·4
(V; X = Bu^t)	90—91 ‡	PhH–Pet †	56·2	7·3	9·3	$C_{14}H_{22}N_2O_3S$	56·4	7·4	9·4
(V; X = *m*-MeO·C_6H_4)§	122—123	EtOH	58·8	5·75	—	$C_{17}H_{20}N_2O_4S$	58·6	5·8	—
(V; X = *p*-Cl·C_6H_4)	144—145	Pr$^i_2$O	54·3	4·7	—	$C_{16}H_{17}ClN_2O_3S$	54·5	4·9	—
(V; X = Ph·S·CH_2)	110 ¶	PhH	56·3	5·5	8·1	$C_{17}H_{20}N_2O_3S_2$	56·0	5·5	7·7
(V; X = Me)	144—145	EtOH	55·3	6·2	—	$C_{13}H_{18}N_2O_3S$	55·3	6·4	—
(VI; X = Et)	101—102	Pr$^i_2$O	56·8	7·1	9·4	$C_{14}H_{20}N_2O_3S$	56·7	6·8	9·45
(VI; X = Bu^t)	192—193	EtOH	59·6	7·5	—	$C_{16}H_{24}N_2O_3S$	59·2	7·5	—
(VI; X = *p*-MeO·C_6H_4	117—118	EtOH	61·1	5·65	—	$C_{19}H_{22}N_2O_4S$	60·9	5·9	—
(VI; X = *m*-MeO·C_6H_4)	137	EtOH	60·8	6·0	—	$C_{19}H_{22}N_2O_4S$	60·9	5·9	—
(VI: X = *p*-Cl·C_6H_4)	160—161	EtOH	56·65	4·85	—	$C_{18}H_{19}ClN_2O_3S$	57·1	5·05	—
(VI; X = Ph·S·CH_2)	179—180	PhH	58·65	5·5	7·1	$C_{19}H_{22}N_2O_3S_2$	58·4	5·7	7·2
(VI; X = Ph·SO_2·CH_2)**	172—173	EtOH	53·8	5·2	7·0	$C_{19}H_{22}N_2O_5S_2$	54·0	5·25	6·6

* Lit.,[11] m. p. 109·5—109·9°. † Light petroleum, b. p. 60—80°. ‡ Metastable, m. p. 78—79°. § From acylethylenediamine. ¶ Metastable, m. p. 106—107°. ** Also obtained by oxidation of the sulphide.

with methylene chloride, and chromatography of the crude product in benzene on alumina gave the pure piperazine (80%), m. p. and mixed m. p. 101—102° (from benzene–light petroleum). With slow heating, the m. p. was 111°. *N*-Acyl derivatives were obtained by the Schotten–Baumann procedure.

Kinetics.—(a) *Alkyl iodide–sodium ethoxide reactions*. Baker's [12] general procedure was followed. Equal volumes of ethanolic solutions of the iodide (*ca.* 0·05M) and of 2N-sodium ethoxide were allowed to attain the temperature (25·0°) of the thermostat during 30 min. Solvolysis of compounds of this type under these conditions is negligible.[2] The solution of sodium ethoxide was then added to the solution of the iodide, the time of half-delivery being taken as zero time. After thorough mixing, aliquot parts (10 ml.) of the solution were removed at intervals and quenched in a mixture of acetic acid (1 ml.) and water (20 ml.). Unchanged organic halide was removed by extraction with benzene (30 ml.) and the benzene extract was washed with water (3 × 20 ml.). Aqueous 0·05N-silver nitrate (10 ml.) was added to the combined aqueous phases and the excess was determined by titration with aqueous 0·05 N-ammonium thiocyanate, with ferric ammonium sulphate in 6N-nitric acid as the indicator. Good rectilinear plots of log $(a - x)$ against t were obtained in all cases, and values of the pseudo-unimolecular rate constants were obtained from the slopes of the graphs. Infinity readings were within 3% of the theoretical values. Results are given in Table 6. A typical series of results is given in Table 3.

(b) *Ester hydrolyses*. The rates of the alkaline hydrolyses at 24·8° of ethyl phenylthioacetate and of ethyl phenylsulphonylacetate were determined by the method of Davies and Evans,[13] their procedure for acid hydrolysis was also used for the former ester. Results are given in

[10] T. S. Moore, M. Boyle, and V. M. Thorn, *J.*, 1929, 39.
[11] L. H. Amundsen and R. I. Longley, *J. Amer. Chem. Soc.*, 1940, **62**, 2811.
[12] J. W. Baker, *J.*, 1932, 1148.
[13] G. Davies and D. P. Evans, *J.*, 1940, 339.

TABLE 3

Rate of displacement of iodide ion from *N*-*m*-methoxybenzoyl-*N*-2-iodoethyl-*N'*-toluene-*p*-sulphonylethylenediamine (IV; X = *m*-MeO·C_6H_4)

Conditions: 0·0125M-iodide and N-sodium ethoxide in ethanol at 25°

t (min.)	10	15	20	25	35	45	55
0·0495M-$AgNO_3$ consumed (ml.)	1·12	1·54	1·85	2·16	2·63	3·05	3·37
$10^3(a - x)$	9·72	8·70	7·93	7·39	6·00	4·96	4·16

k [from plot of log $(a - x)$ against *t*] = 0·0186 min.$^{-1}$

Duplicate *k* = 0·0188 min.$^{-1}$

Table 4. Acid hydrolysis of the latter ester, however, gave very erratic results. The high readings initially obtained decreased irregularly during runs and divergence between experimental and theoretical (blank) t_0 readings increased with increasing initial concentrations of the ester. Similar behaviour was encountered when different specimens of the ester were used. No explanation is offered for these results.

TABLE 4

Rates of ester hydrolysis

Ester	Conditions	*k* (l. mol.$^{-1}$ sec.$^{-1}$)
Ph·S·CH_2·CO_2Et	Acid	8·21 × 10^{-6}
Ph·S·CH_2·CO_2Et	Alkaline	0·385
Ph·SO_2·CH_2·CO_2Et	Alkaline	0·846

RESULTS AND DISCUSSION

In considering the reactions of the amido-iodides with sodium ethoxide, we examined first the effect of change in the acylamino-group upon the product distribution. The reaction conditions (0·05M-amide in ethanolic N-sodium ethoxide at 78°) were chosen so as to allow direct comparison with previous results.[2] Products are listed in Table 5; the quoted yields of olefin are actually those of *N*-acyl-*N'*-toluene-*p*-sulphonylethylenediamines produced from the olefins (III) by acid hydrolysis during working up.[1] No ethoxy-compounds (I; Y = NTs, Z = OEt) were obtained. It can be seen that, broadly speaking, the stronger the acid X·CO_2H, the greater the yield of cyclisation product. Particularly convincing in this respect is the change from almost complete olefin formation in the pivaloyl compound to almost complete cyclisation in the phenylsulphonyl compound. The general conclusion reached in Part III with respect to the inductive effects on the amido-group is thus confirmed.

TABLE 5

Products (%) obtained from iodides (IV)

X	Piperazine *	Olefin	Acid	Reaction time (min.)
Bu^t	1·0	92·4	†	12
Et	18·6	70·6	†	12
Me	31·8	57·5	†	12
p-MeO·C_6H_4	38·8(41·2)	48·5	2·4	12
Ph	54·9(62·6)	34·4	8·3	12
m-MeO·C_6H_4OMe	55·7(64·2)	31·7	8·3	12
p-Cl·C_6H_4	46·2(76·7)	18·6	30·7	12
Ph·S·CH_2	70·5(83·9)	9·9	13	12
Ph·SO_2·CH_2	90·0	0	0	6

* Yields in parentheses corrected for alcoholysis. † Acid not determined.

The marked effect of the acylamino-group prompted us to determine whether a quantitative relationship between the rate of cyclisation and the structure of the acylamino-group existed. Overall rates of reaction of the iodides with sodium ethoxide at 25° were

measured by following the release of iodide ion. In principle, the iodide ion is the product of three concurrent reactions: cyclisation, elimination, and external substitution, *i.e.*,

$$k_{obs} = k_{cyclisation} + k_{elimination} + k_{substitution} \quad (1)$$

It was shown earlier [1] that the simple iodide (VII), under comparable conditions, gave 94% of elimination and only traces of ethoxy-compound derived from substitution. Only small amounts of ethoxy-compounds could have been formed from the amido-iodides (Table 5), and if external substitution is neglected equation (1) becomes

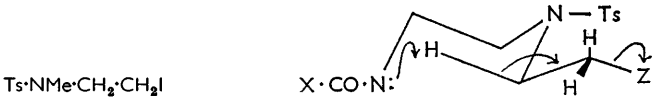
$$k_{obs} = k_c + k_e \quad (2)$$

A further simplification is possible if it is assumed that the rate constant for elimination is the same for all the amido-iodides, *i.e.*,

$$k_{obs} = k_c + \text{constant} \quad (3)$$

This assumption appears reasonable on the following grounds. Elimination in the simple iodide (VII), which lacks an acylamino-group, is strongly promoted [1] by the β-toluene-*p*-sulphonamido-group; simple straight-chain primary halides give relatively little elimination under these conditions.[14] Any effect of the distant acylamino-group would be superimposed upon the effect of the sulphonamido-group, so that the differential effect of change in the acylamino-group should be small. This superimposed effect may, however, account for the fact that, while the pivaloyl compound and the simple iodide both give more than 90% elimination, the former reacts faster by a factor of 1·6.

The possibility exists that elimination is caused not only by the external base (EtO^-) but also by the ionised acylamino-group acting as an " internal " base (cf. VIII). As the acylamino-group is also involved in cyclisation, however, it would be expected that any effects on the acylamino-group which promote cyclisation should also promote elimination. It can be seen from Tables 5 and 6 that a low rate of overall reaction is associated with a large extent of elimination. Significant direct participation by the acylamino-group in elimination is, therefore, improbable.



(VII) (VIII)

In correlating the rates of cyclisation with the structure of the acylamino-group, the value of the constant in equation (3) has been taken as the rate constant (k') for elimin-

TABLE 6

Pseudo-unimolecular rate constants (min.$^{-1}$) for reactions of iodides with ethanolic N-sodium ethoxide at 25°

Iodide	k (mean) × 10^2	σ^* for X	Iodide	k (mean) × 10^2	σ^* for X
(VII)	0·42	—	(IV; X = Ph)	1·84	+0·600
(IV; X = Bu^t)	0·68	−0·300	(IV; X = *m*-MeO·C_6H_4)	1·87	+0·62
(IV; X = Et)	0·86	−0·100	(IV; X = Ph·S·CH_2) ...	2·07	+0·66
(IV; X = Me)	0·85	0·0	(IV; X = *p*-Cl·C_6H_4) ...	2·60	+0·92
(IV; X = *p*-MeO·C_6H_4)	1·47	+0·42	(IV; X = Ph·SO_2·CH_2)	5·43	+1·37

ation in the iodide (VII) with the reservation that this value is probably too low. Re-writing equation (3)

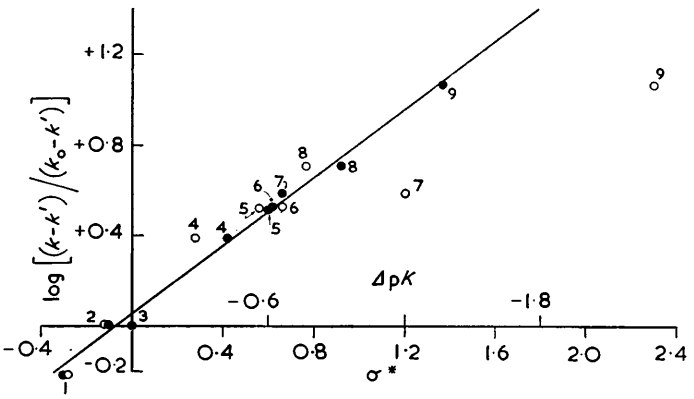
$$k_c = k_{obs} - k' \quad (4)$$

[14] C. K. Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, Section 31c.

In an initial attempt to find a relationship between the rate of cyclisation and a parameter characteristic of the acylamino-group, the relationship expressed in equation (5) was examined

$$\log[(k - k')/(k_0 - k')] = \alpha(pK_{a(x)} - pK_{a(Me)}) \quad (5)$$

Where k is the observed rate constant, k_0 is the rate constant for the iodide (IV; X = Me), and $pK_{a(x)}$ refers to the dissociation constant of the acid $X{\cdot}CO_2H$. The plot (see Figure)



Plots of $\log \frac{(k - k')}{(k_0 - k')}$ against σ* (●) and $(pK - pK_0)$ (○)

1, Bu^t. 2, Et. 3, Me. 4, *p*-MeO·C_6H_4. 5, Ph. 6, *m*-MeO·C_6H_4. 7. Ph·S·CH_2. 8, *p*-Cl·C_6H_4. 9, Ph·SO_2·CH_2

of equation (5) shows a poor correlation. This was not entirely unexpected, since reaction-series with similar variations in substituent show similar behaviour.[15]

The failure of this simple expression led us to examine the applicability of the Taft free energy relationship

$$\log (k/k_0) = \rho^*\sigma^*$$

Where

$$\sigma^* = \frac{1}{2{\cdot}48}[\log (k/k_0)_B - \log (k/k_0)_A] \quad (6)$$

The terms $(k/k_0)_B$ and $(k/k_0)_A$ refer to the rates of hydrolysis of esters ($X{\cdot}CO_2R$) under basic and acidic conditions, respectively, relative to acetates. σ* values were available[16] for substituents in $X{\cdot}CO_2R$ where X = Ph, Et, and Bu^t. Values of σ* for *p*-Cl·C_6H_4, *p*-MeO·C_6H_4, and *m*-MeO·C_6H_4 were calculated from literature data. Mean rates of basic hydrolysis of esters of aromatic acids at 25° reported by several groups are given by Jones and Robinson,[17] and these were taken in conjunction with mean values of $(k_{Ph}/k_{Me})_B$ given by Taft.[18] Data for acid catalysed reactions were taken from reported [19] rates of esterification with methanol at 25°. The rate of the acid-catalysed esterification of *p*-chlorobenzoic acid shows a considerable deviation from the Hammett relationship for this reaction and, if this rate is " corrected," a value of σ* = 0·88 is obtained. The directly calculated value (Table 6) has, however, been used in the Figure.

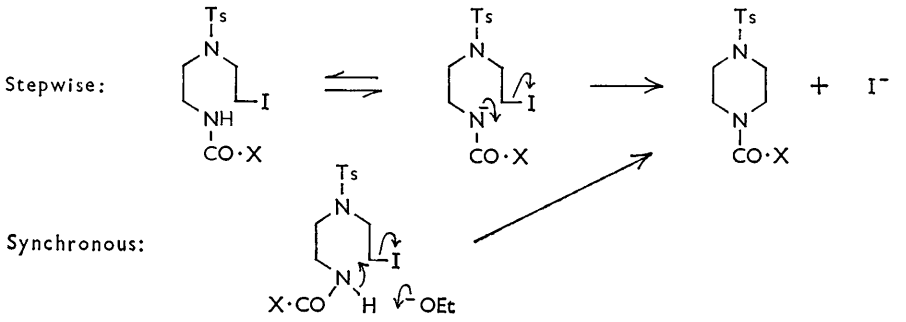
No hydrolysis data were available for phenylthio- or phenylsulphonyl-acetates. σ*

[15] R. W. Taft in " Steric Effects in Organic Chemistry," ed. M. S. Newman, Wiley, New York, 1956, p. 584.
[16] Ref. 15, p. 591.
[17] B. Jones and J. Robinson, *J.*, 1955, 3845.
[18] R. W. Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 2729.
[19] R. J. Hartmann and A. M. Borders, *J. Amer. Chem. Soc.*, 1937, **59**, 2107; R. J. Hartmann and A. G. Gassmann, *ibid.*, 1940, **62**, 1559.

for phenylthiomethyl was obtained directly by measurement of the rates of basic and acid hydrolysis of the ethyl ester. These, in conjunction with appropriate data for acetates [13] gave [from equation (6)] the value $\sigma^* = +0{\cdot}66$. An attempt to obtain σ^* for phenylsulphonylmethyl in a similar way was frustrated by our failure to obtain satisfactory results for the acid hydrolysis of ethyl phenylsulphonylacetate. Ionisation constants of acids have, however, been related [20] to σ^* ($\rho^* = 1{\cdot}72$); the dissociation constant of phenylsulphonylacetic acid [21] leads to a value of $\sigma^* = 1{\cdot}37$.

The plot of the left hand side of equation (5) against σ^* is shown in the Figure. When the assumptions that have been made are taken into account, the rectilinearity is satisfactory.

The reactions under consideration require the presence of bases if they are to proceed at an appreciable rate.[2] This implies that removal of the proton of the amido-group occurs either before, or synchronously with, cleavage of the carbon–iodine bond. The plausible mechanisms are represented as follows:



These alternatives are analogous to β-elimination by E_1cb and by E_2 mechanisms, respectively. If ionisation is fully developed, as in the stepwise mechanism, electron-withdrawing groups, while increasing the acidity of the amido-group, will reduce the nucleophilicity of the resulting ion. In this connection, Scott and Flynn [22] have studied the base-catalysed cyclisation of 2-arenesulphonamidoethyl chlorides to arenesulphonylaziridines. They find that these reactions, which clearly involve pre-ionisation of the acidic sulphonamido-group, follow first order kinetics and give a *negative* value of $\rho = -0{\cdot}93$. By contrast, the cyclisations of the very much less acidic 2-chloroethyl-*N*-arylurethanes,[23] in ethanolic sodium ethoxide, follow second order kinetics and give a *positive* value of $\rho = +1{\cdot}72$. The positive value of $\rho^* = 0{\cdot}8$ obtained in our system thus leads us to favour the synchronous mechanism; the lower sensitivity towards polar effects (expressed by ρ^*) is understandable, because the polar group is more remote from the nucleophilic site. Furthermore, the value of ρ^* is very much less than for the ionisation of carboxylic acids, suggesting that the degree of N–H bond cleavage in the transition state is low.

The parameter σ^* gives a measure of the polar effect of a group uncomplicated by resonance or steric effects. The rectilinearity of the Taft plot for this reaction series indicates that resonance effects and, surprisingly, steric effects, are unimportant in determining the rates of cyclisation.

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[20] Ref. 15, p. 607.
[21] H. D. Crockford and T. B. Douglas, *J. Amer. Chem. Soc.*, 1934, **56**, 1472.
[22] F. L. Scott and E. Flynn, *Tetrahedron Letters*, 1964, 1675.
[23] F. L. Scott and D. F. Fenton, *Tetrahedron Letters*, 1964, 1681.