714. *Intramolecular Reactions of Amides. Part III.*[1] *Cyclisation* versus *Elimination and Replacement in Derivatives of ω-Amido-alcohols.*

By C. J. M. Stirling.

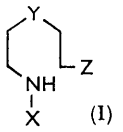
A series of *N*-substituted benzamides, toluene-*p*-sulphonamides, and *p*-bromobenzenesulphonamides has been prepared with ω-leaving groups and various structures of the chain linking the amido-group and the leaving group. The products obtained from them on treatment with ethanolic sodium ethoxide have been examined with respect to the competition between cyclisation, external substitution (by EtO^-), and elimination.

The sulphonamides, with one accountable exception, give only cyclic products irrespective of variation of the leaving group and the chain structure. The extent of cyclisation of the benzamides is insensitive to the leaving group but depends upon the chain structure in a manner which suggests that inductive strengthening of the acidity of the benzamido-group is important. Exceptional behaviour is encountered when sulphur is present in the chain and reasons for this are advanced.

Cyclisation, under basic conditions, of amides with an ω-leaving group has frequently been observed [1, 2] and applied in heterocyclic synthesis,[3, 4] but no systematic investigation of the effects of structure in the amido-group, the chain of atoms linking it to the leaving

[1] Part II, Stirling, *J.*, 1960, 255.
[2] Bennett and Hafez, *J.*, 1941, 652.
[3] Lipp and Caspers, *Ber.*, 1925, **58**, 1011.
[4] Dobson and Raphael, *J.*, 1958, 3642.

group, or the leaving group itself, has been made. In the present work, the products obtained from a series of amides of general structure (I) under standard basic conditions (0·2M-amide in ethanolic N-sodium ethoxide at 78°) have been examined. The series includes the compounds (I) in which X, Y, and Z were as shown in the key (not all the possible combinations have been studied). The results are presented in Table 4 and are discussed in a later section of the paper. Peacock and Gwan [5] previously obtained 1,4-di-toluene-*p*-sulphonylpiperazine from the chloride (IC) by treatment with ethanolic sodium ethoxide or ethylenediamine in yields of 82% and 97%, respectively.



(I)

	X	Y	Z
IA	Ts	NTs	OTs
IB	Ts_2	NTs	OTs
IC	Ts	NTs	Cl
ID	Bz	NTs	OTs
IE	Bz	NTs	I
IF	Bz	NTs	Cl
IG	Bz	O	Cl
IH	Bz	O	I
IJ	Bz	CH_2	Cl
IK	Bz	CH_2	I

	X	Y	Z
IL	BrS	O	Cl
IM	BrS	O	I
IN	Ts	CH_2	Cl
IO	BrS	CH_2	Cl
IP	Ts	CH_2	OTs
IQ	Bz	S	Cl
IR	Bz	SO	Cl
IS	Bz	SO_2	Cl
IT	Ts	SO_2	Cl

(Ts = *p*-$C_6H_4Me{\cdot}SO_2$; BrS = *p*-$C_6H_4Br{\cdot}SO_2$)

Preparation of Materials.—Series Y = $>N{\cdot}C_6H_4Me$-*p*. The starting material for this series was *N*-2-hydroxyethylethylenediamine (II), toluene-*p*-sulphonylation of which yielded the amido-esters (IA) and (IB) and thence the chloride (IC). The *N*-benzamido-compounds were obtained by the reactions outlined in the scheme:

$$NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH\ (II) \xrightarrow{1} Bz{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NBz{\cdot}CH_2{\cdot}CH_2{\cdot}OH \xrightarrow{2}$$

$$Bz{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}OBz \xrightarrow{3} Bz{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NTs{\cdot}CH_2{\cdot}CH_2{\cdot}OBz \xrightarrow{4}$$

$$Bz{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NTs{\cdot}CH_2{\cdot}CH_2{\cdot}OH\ (III) \qquad (Ts = p\text{-}C_6H_4Me{\cdot}SO_2)$$

Reagents: 1, BzCl–NaOH; 2, $SOCl_2$; 3, TsCl–pyridine; 4, KOH–EtOH.

Toluene-*p*-sulphonylation of the hydroxy-diamide (III) gave the mixed derivative (ID), readily converted, by treatment with appropriate inorganic halides in aprotic solvents, into the iodo- (IE) and chloro-derivative (IF).

Series Y = O *and* CH_2. The key compound in the oxygen series, the chloro-ether (IG), obtained by ring-opening of 4-benzoylmorpholine with phosphorus pentachloride, gave the iodide (IH) on treatment with sodium iodide, and on acid hydrolysis the base which was converted into the *p*-bromobenzenesulphonamides (IL) and (IM).

N-5-Chloro- [6] (IJ) and *N*-5-iodo-pentylbenzamide [7] (IK) were known. Acid hydrolysis of the former and treatment of the base with the appropriate sulphonyl chloride gave the sulphonamides (IN) and (IO). The *p*-bromobenzenesulphonyl derivative (IO) was prepared for comparison with the oxygen series in which a crystalline toluene-*p*-sulphonamide chloride was not obtained. The toluene-*p*-sulphonate (IP) was obtained directly from 5-aminopentanol.

Series X = S, SO, *and* SO_2. The chloro-sulphides (IV) were obtained by the route:

$$X{\cdot}NH{\cdot}CH_2{\cdot}CH_2Br \xrightarrow{1,2} X{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}SH \xrightarrow{3} X{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2Cl\ (IV)$$

X = Bz (IQ) or Ts.

Reagents: 1, $SC(NH_2)_2$; 2, aq.NaOH; 3, $Cl{\cdot}CH_2{\cdot}CH_2Cl$–NaOEt.

Partial or complete oxidation gave the sulphoxide (IR) or the sulphones (IS) and (IT).

[5] Peacock and Gwan, *J.*, 1937, 1468.
[6] von Braun, *Ber.*, 1904, **37**, 2915.
von Braun and Steindorff, *Ber.*, 1905, **38**, 169.

TABLE 1.

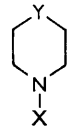
ω-Halogeno- and ω-toluene-*p*-sulphonyloxy-amides.

Amide	Cryst.* from	M. p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
IA	$COMe_2$–EtOH	147—148°	77	53·1	5·4	4·7	$C_{25}H_{30}N_2O_7S_3$	52·9	5·3	5·0
IC [5]	MeOH	110—111	53	50·0	5·4	6·4	$C_{18}H_{23}ClN_2O_4S_2$	50·1	5·3	6·5
ID	EtOH	108	89	58·3	5·2	4·9	$C_{25}H_{28}N_2O_6S_2$	58·1	5·4	5·4
IE	EtOH	101—102	93	45·4	4·7	—	$C_{18}H_{21}IN_2O_3S$	45·7	4·45	—
IF	MeOH	138—139	85	56·7	5·4	7·3	$C_{18}H_{21}ClN_2O_3S$	56·7	5·5	7·4
IH	C_6H_6–Pet	48·5	100	41·7	4·65	—	$C_{11}H_{14}INO_2$	41·4	4·4	—
IJ [6]	Et_2O	60	40	63·5	7·2	6·6	$C_{12}H_{16}ClNO$	63·9	7·1	6·2
IK [7]	Et_2O–Pet	54	97	45·6	5·15	—	$C_{12}H_{16}INO$	45·4	5·0	—
IL	Et_2O	83—85	65	34·6	3·6	—	$C_{10}H_{13}BrClNO_3S$	35·1	3·8	—
IM	EtOH	74—75	53	27·8	3·3	—	$C_{10}H_{13}BrINO_3S$	27·7	3·0	—
IN	Et_2O	61—62	87	52·3	6·6	5·2	$C_{12}H_{18}ClNO_2S$	52·4	6·5	5·1
IO	EtOH	64—66	70	38·9	4·55	—	$C_{11}H_{15}BrClNO_2S$	38·6	4·4	—
IP	C_6H_6–Pet	86—87	71	56·1	5·9	3·5	$C_{19}H_{25}NO_5S_2$	55·5	6·1	3·4
IR	C_6H_6	118—119	88	50·9	5·3	13·6 †	$C_{11}H_{14}ClNO_2S$	50·9	5·4	13·7 †
IS	$CHCl_3$	137·5	94	48·0	5·3	5·1	$C_{11}H_{14}ClNO_3S$	48·0	5·1	5·1

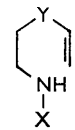
* Pet = Light petroleum (b. p. 40—60°). † Analysis for Cl.

TABLE 2.

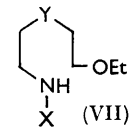
Reference compounds.



(V)



(VI)



(VII)

Compound	Starting material	Solvent for crystn.	M. p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
Bz·NH·CH_2·CH_2·NHTs	Bz·NH·CH_2·CH_2·$NH_3^+Cl^-$ [8]	C_6H_6	136—137° *	70	60·5	6·05	8·7	$C_{16}H_{18}N_2O_3S$	60·3	5·65	8·8
V; X = Bz, Y = NTs	V; X = H, Y = NBz [9]	EtOH	170—171	47	63·0	5·75	—	$C_{18}H_{20}N_2O_3S$	62·8	5·8	—
VII; X = Bz, Y = SO	VII; X = Bz, Y = S	C_6H_6–Pet(*a*)	90	92	58·1	6·95	5·3	$C_{13}H_{19}NO_3S$	58·0	7·1	5·2
VII; X = Bz, Y = SO_2	VII; X = Bz, Y = S	C_6H_6	113—114	96	54·85	6·85	4·75	$C_{13}H_{19}NO_4S$	54·7	6·7	4·9
V; X = Bz, Y = S	V; X = H, Y = S [10]	Pet(*b*)	63	76	64·2	6·5	7·2	$C_{11}H_{13}NOS$	63·8	6·3	6·8
V; X = Bz, Y = SO_2	V; X = Bz, Y = S	EtOH	172—173	84	55·65	5·7	—	$C_{11}H_{13}NO_3S$	55·2	5·45	—
V; X = Ts, Y = S	V; X = H, Y = S	EtOH	126	74	51·2	5·3	—	$C_{11}H_{15}NO_2S_2$	51·4	5·8	—
V; X = Ts, Y = SO_2	V; X = Ts, Y = S	EtOH	201—202	88	45·4	4·9	—	$C_{11}H_{15}NO_4S_2$	45·7	5·2	—
VII; X = Ts, Y = S	Ts·NH·CH_2·CH_2·SH	—	*c*	96	51·2	6·85	—	$C_{13}H_{21}NO_3S_2$	51·5	6·95	—
VII; X = Ts, Y = SO_2	VII; X = Ts, Y = S	—	*d*	75	46·5	6·65	—	$C_{13}H_{21}NO_5S_2$	46·6	6·3	—
VI; X = Bz, Y = CH_2 [11]	IK	—	*e*	60	75·9	8·0	—	$C_{12}H_{15}NO$	76·1	7·9	—
VII; X = Bz; Y = CH_2 [12]	IJ	—	*f*	62	71·5	9·0	—	$C_{14}H_{21}NO_2$	71·5	8·9	—

* Lit.,[13] m. p. 135°. Pet (*a*) = Light petroleum (b. p. 40—60°). Pet (*b*) = Light petroleum (b. p. 60—80°). (*c*) B. p. 194°/0·01 mm., n_D^{18} 1·5438. (*d*) B. p. 240°/0·05 mm., n_D^{18} 1·5316. (*e*) B. p. 120°/0·05 mm., n_D^{18} 1·5445. (*f*) B. p. 160°/0·7 mm., n_D^{20} 1·5182.

Experimental

Extracts were dried over anhydrous Na_2SO_4. The light petroleum used had b. p. 40—60°. Ethanolic N-sodium ethoxide, freshly prepared from ethanol containing 0·34% w/v of water, was used unless otherwise stated.

General Procedures.—(*a*) *Halides.* (i) Chlorides. The toluene-*p*-sulphonate (1 mol.) and lithium chloride (10 mol.) in butanone (5 vol.) and t-butyl alcohol (1 vol.) were refluxed for 40 hr. Dilution of the mixture with water and extraction with chloroform gave the product.

(ii) Iodides. The toluene-*p*-sulphonate or chloride (1 mol.) and sodium iodide (5 mol.) in ethanol were refluxed for 6 hr., and the mixture was then treated as for the chloride.

(*b*) *Sulphides.* The thiol (1 mol.) in ethanolic sodium ethoxide (1 mol.) was refluxed with the halide (1·2 mol.) for 1 hr. Dilution with water, acidification, and extraction with chloroform gave the product.

(*c*) *Sulphoxides.* The sulphide (1 mol.) in acetone was treated with 30% hydrogen peroxide (1·25 mol.). The mixture was kept at 20° for 36 hr., then dilution with water and extraction with chloroform yielded the product.

(*d*) *Sulphones.* The sulphide (1 mol.), in acetic acid, was heated with 30% hydrogen peroxide (4 mol.) at 90° for 1 hr. The mixture was diluted with water, neutralised with sodium hydrogen carbonate, and extracted with chloroform.

(*e*) *Conversion of benzamides into sulphonamides.* The amide (1 mol.) was refluxed with concentrated hydrochloric acid (15 mol.) for 24 hr. The solution was diluted with water and extracted with ether. The aqueous layer was evaporated to dryness under reduced pressure at 40° and the residue was treated with the appropriate sulphonyl halide under Schotten–Baumann conditions.

(*f*) *Treatment of amides with sodium ethoxide.* The ω-halogeno(or toluene-*p*-sulphonyloxy)-amide was treated with ethanolic sodium ethoxide so as to give a 0·2M-solution of amide, which was kept at 78° until reaction was complete. Unless otherwise stated, three volumes of saturated brine were added to the mixture which was acidified with hydrochloric acid and extracted with chloroform. The extracts were washed with aqueous sodium hydrogen carbonate, dried, and evaporated. Benzoic acid was isolated from the aqueous extracts by acidification and extraction with methylene chloride.

These procedures are illustrated by the examples given below and details of other compounds are collected in Tables 1, 2, and 4.

Reaction of N-2-*Toluene*-p-*sulphonyloxyethyl*-NN′-*ditoluene*-p-*sulphonylethylenediamine* (IA) *with Triethylamine.*—The amide (1·0 g.) was added to triethylamine (5 ml.) in ethanol (20 ml.), and the mixture was refluxed for 2½ hr. Filtration gave a residue of 1,4-ditoluene-*p*-sulphonylpiperazine (0·50 g., 70%) and evaporation of the filtrate gave recovered amido-ester (0·18 g., 18%), m. p. and mixed m. p. 141—142°.

N-*Toluene*-p-*sulphonyloxyethyl*-NN′N′-*tritoluene*-p-*sulphonylethylenediamine* (IB).—*N*-2-Hydroxyethylethylenediamine (10 g.), in 15% aqueous sodium hydroxide (100 ml.), was treated with toluene-*p*-sulphonyl chloride (38 g.) in acetone. When reaction was complete. the mixture was filtered and the residue was extracted with chloroform. Evaporation of the extracts gave the *amido-ester* (7·5 g.), m. p. 166—168°, raised to 170—171° by crystallisation from acetone (Found: C, 53·1; H, 5·05; N, 3·6. $C_{32}H_{36}N_2O_9S_4$ requires C, 53·4; H, 5·0; N, 3·9%).

NN′-*Dibenzoyl*-N-2-*hydroxyethylethylenediamine.*—*N*-2-Hydroxyethylethylenediamine (30 g.) in 10% aqueous sodium hydroxide was treated with benzoyl chloride (75 g.). The mixture was acidified and extracted with chloroform. Evaporation of the extracts gave the *hydroxy-diamide* (57 g.), m. p. 136° (from ethanol–ether) (Found: C, 68·6; H, 6·2; N, 9·4. $C_{18}H_{20}N_2O_3$ requires C, 69·2; H, 6·4; N, 9·0%). Benzoylation (in pyridine) of the hydroxy-diamide gave the *benzoate*, m. p. 119—120° (from acetone) (Found: C, 72·7; H, 5·4; N, 6·7. $C_{25}H_{24}N_2O_4$ requires C, 72·7; H, 5·8; N, 6·7%).

[8] Hill and Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 822.
[9] Moore, Boyle, and Thorn, *J.*, 1929, 39.
[10] Cymerman-Craig and Tate, *Chem. and Ind.*, 1954, 1455.
[11] von Braun, *Ber.*, 1910, **43**, 2864.
[12] von Braun, *Ber.*, 1909, **42**, 1429.
[13] Peacock and Dutta, *J.*, 1934, 1303.

N-*Benzoyl*-N′-2-*benzoyloxyethylethylenediamine Hydrochloride*.—The preceding hydroxyamide (54 g.) was added to thionyl chloride (60 ml.) at 0°. After 1 hr. the excess of thionyl chloride was removed *in vacuo*, and the residue was boiled with water for 30 min. The mixture was extracted with benzene, and concentrated hydrochloric acid (15 ml.) was added to the aqueous layer which was evaporated to dryness. Trituration of the residue with ether gave the *hydrochloride* (46 g.), m. p. 139—140°, raised to 145—146° by crystallisation from ethanol–acetone (Found: C, 61·9; H, 5·8; N, 8·0. $C_{18}H_{21}ClN_2O_3$ requires, C, 62·0; H, 6·0; N, 8·0%).

N′-*Benzoyl*-N-2-*benzoyloxyethyl*-N-*toluene*-p-*sulphonylethylenediamine*.—The preceding hydrochloride (46 g.) was treated with an excess of aqueous sodium carbonate, and the liberated base was quickly extracted with chloroform. After evaporation of the extracts, the residue was treated in pyridine (100 ml.) with toluene-*p*-sulphonyl chloride (33 g.). After 2 hr., addition of water and extraction with chloroform gave the *sulphonamide* (51 g.), m. p. 101—102° (from ethanol) (Found: C, 64·5; H, 5·5; N, 5·7. $C_{25}H_{26}N_2O_5S$ requires C, 64·4; H, 5·6; N, 6·0%).

N′-*Benzoyl*-N-2-*hydroxyethyl*-N-*toluene*-p-*sulphonylethylenediamine* (III).—The preceding amido-ester (51 g.) was refluxed with potassium hydroxide (9 g., 1·5 mol.) in 80% aqueous ethanol (300 ml.) for 1 hr. Acidification of the mixture and extraction with chloroform gave the *amido-alcohol* (36·5 g.), m. p. 125—126° (from ethanol) (Found: C, 59·9; H, 6·2; N, 7·4. $C_{18}H_{22}N_2O_4S$ requires C, 59·6; H, 6·1; N, 7·7%).

Reactions of N′-*benzoyl*-N-2-*halogenoethyl*-N-*toluene*-p-*sulphonylethylenediamines* (IG and IF) *with Sodium Ethoxide*.—The iodide (2·745 g.) was treated with ethanolic sodium ethoxide, and addition of ethanol to the product gave the piperazine (1·260 g.), m. p. and mixed m. p. 165—168°. Treatment of the mother-liquors as in the experiment with the chloride (below) gave further piperazine (0·045 g.), m. p. and mixed m. p. 168—170°, and *N*-benzoyl-*N*′-toluene-*p*-sulphonylethylenediamine (0·475 g.), m. p. and mixed m. p. 135—137°. In a subsequent experiment with the amide (10 g.), acidification was omitted and extraction was with methylene chloride. The extracts were evaporated and treatment of the residue with ethanol yielded the piperazine (4·590 g.), m. p. and mixed m. p. 165—168°. The mother-liquors gave N′-*benzoyl*-N-*toluene*-p-*sulphonyl*-N-*vinylethylenediamine* (2·225 g.), m. p. 96—97°, raised to 104—105° by chromatography on alumina in benzene solution (Found: C, 62·7; H, 6·0; N, 8·65. $C_{18}H_{20}N_2O_3S$ requires C, 62·8; H, 5·8; N, 8·2%). The olefin (85 mg.), in methanol (30 ml.), was treated with concentrated sulphuric acid (0·1 ml.). The solution was distilled into methanolic 2,4-dinitrophenylhydrazine sulphate; acetaldehyde 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 167—168°, was obtained by chromatography of the crude derivative on alumina. The residual solution was neutralised with aqueous sodium hydrogen carbonate and extraction with methylene chloride gave *N*-benzoyl-*N*′-toluene-*p*-sulphonylethylenediamine (75 mg., 95%), m. p. and mixed m. p. 136—137°.

The chloride (13·87 g.), with ethanolic sodium ethoxide, gave a product which, on addition of ethanol (15 ml.), afforded *N*-benzoyl-*N*′-toluene-*p*-sulphonylpiperazine (7·390 g.), m. p. and mixed m. p. 170—171°. The mother-liquors were evaporated and the residue, in benzene, was extracted with 5% aqueous sodium hydroxide. Evaporation of the organic layer and treatment of the residue with ether gave more of the piperazine (0·340 g.), m. p. and mixed m. p. 163—166°. The aqueous extracts were acidified, and extraction with methylene chloride gave *N*-benzoyl-*N*′-toluene-*p*-sulphonylethylenediamine (2·200 g.), m. p. 117°, alone or mixed with an authentic specimen (higher-melting form, Table 2). Benzoic acid (0·660 g.), m. p. and mixed m. p. 122°, was obtained from the sodium hydrogen carbonate extracts.

N-2-2′-*Ethoxyethylthioethylbenzamide*.—*N*-2-Mercaptoethylbenzamide [14] (7 g.) in ethanolic sodium ethoxide (1 mol.) was treated with 2-ethoxyethyl bromide [15] (6 g.). The mixture was refluxed for 1 hr., diluted with water, and acidified. Extraction with chloroform gave the *sulphide* (8 g.), b. p. 160°/0·01 mm., n_D^{20} 1·5513 (Found: C, 61·9; H, 7·05. $C_{13}H_{19}NO_2S$ requires C, 61·7; H, 7·5%).

N-2-*Mercaptoethyltoluene*-p-*sulphonamide*.—*N*-2-Bromoethyltoluene-*p*-sulphonamide [13] (69 g.) was refluxed for 2 hr. with thiourea (19 g.) in ethanol (100 ml.). Addition of ethyl acetate precipitated the *isothiouronium salt* (73·5 g.), m. p. 186° (from ethanol–ethyl acetate) (Found: C, 34·2; H, 4·8; N, 11·7. $C_{10}H_{16}BrN_3O_2S_2$ requires C, 33·9; H, 4·5; N, 11·9%). The salt

[14] Stirling, *J.*, 1958, 4524.
[15] *Org. Synth.*, Coll. Vol. III, p. 370.

(10 g.), suspended in water (100 ml.), was treated with 10% aqueous sodium hydroxide (35 ml.). After 15 min. the mixture was filtered, acidified, and extracted with chloroform. Evaporation of the extracts gave the *thiol* (6·2 g.), m. p. 49—50° (from benzene–light petroleum) (Found: C, 46·7; H, 5·6; N, 6·1. $C_9H_{13}NO_2S_2$ requires C, 46·9; H, 5·1; N, 6·0%).

N-2-2′-*Chloroethylthioethylbenzamide* (IQ).—*N*-2-Mercaptoethylbenzamide (50 g.) in ethylene dichloride (330 ml.) was added to ethanolic sodium ethoxide (1 mol.). The mixture was refluxed for 30 min. and poured into water. Extraction with chloroform gave the crude chloro-sulphide (64 g.), m. p. 63—65°, which, on the addition of ether, left 1,2-*di*-(2-*benzamidoethylthio*)*ethane*, m. p. 144—145° (from benzene) (Found: C, 61·8; H, 6·4; N, 7·05. $C_{20}H_{24}N_2O_2S_2$ requires C, 61·8; H, 6·1; N, 7·1%). Evaporation of the ethereal extracts gave the *chloro-sulphide*, m. p. 70° (from benzene–light petroleum) (Found: C, 54·8; H, 6·0. $C_{11}H_{14}ClNOS$ requires C, 54·5; H, 5·8%). The chloro-sulphide (2·74 g.), after treatment with ethanolic sodium ethoxide, was poured into brine and, without acidification, was extracted with methylene chloride. The extracts were evaporated and the residue, in benzene, was poured on an alumina column (50 g., 2 cm.). Elution with benzene (1500 ml.) gave N-2-*vinylthioethylbenzamide* (1·815 g.), m. p. 64° (from ether–light petroleum) (Found: C, 63·9; H, 6·5; N, 6·5%). The m. p. was depressed on admixture with 4-benzoylthiomorpholine. Further elution with chloroform gave a product which, when oxidised with 30% hydrogen peroxide (5 ml.) in acetic acid (10 ml.) at 100° for 1 hr., afforded *N*-2-2′-ethoxyethylsulphonylethylbenzamide (0·15 g.), m. p. 109—110° alone or mixed with an authentic specimen.

Treatment of the vinyl sulphide with hydrogen peroxide in acetic acid gave the *vinyl sulphone*, m. p. 70° (from benzene–light petroleum) (Found: C, 55·8; H, 5·8%). Treatment of this sulphone (400 mg.) with cold ethanolic sodium ethoxide gave the 2-ethoxyethyl sulphone (450 mg.), m. p. 113° (from benzene) alone or mixed with an authentic specimen. Hydrolysis of the vinyl sulphide with methanolic sulphuric acid gave acetaldehyde (2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 167—168°) and *N*-2-mercaptoethylbenzamide, identified as the *S*-2,4-dinitrophenyl derivative, m. p. and mixed m. p. 192—193° (from acetone) (lit.,[16] m. p. 185°) (Found: N, 12·0. Calc. for $C_{15}H_{13}N_3O_5S$: N, 12·1%).

N-2-2′-*Chloroethylsulphonylethyltoluene*-p-*sulphonamide* (IT).—*N*-2-Mercaptoethyltoluene-*p*-sulphonamide in 2% ethanolic sodium ethoxide (1 mol.) and ethylene dichloride (20 mol.) was refluxed for 45 min. Dilution with water and extraction with chloroform gave a product which was extracted with ether, leaving a residue which was not further investigated. Evaporation of the ether extracts gave the crude (liquid) chloro-sulphide, oxidation of which, with an excess of hydrogen peroxide in acetic acid, gave the *sulphone*, m. p. 126° (from benzene–light petroleum) (Found: C, 41·0; H, 5·1. $C_{11}H_{16}ClNO_4S_2$ requires C, 40·5; H, 4·9%). Treatment of the sulphone (985 mg.) with ethanolic sodium ethoxide gave a product (1050 mg.) whence treatment with ether precipitated 4-toluene-*p*-sulphonylthiomorpholine 1,1-dioxide (40 mg. 4·5%), m. p. and mixed m. p. 195—200°. Evaporation of the extracts gave a residue (1010 mg.), n_D^{18} 1·5302, which on distillation gave the ethoxy-sulphone (890 mg. 88%), b. p. 240°/0·01 mm. n_D^{18} 1·5293. When the time of heating was reduced to 5 sec., the yield of cyclic sulphone was 14%, and that of ethoxy-sulphone 74%.

Ring-opening of 4-*Toluene*-p-*sulphonylthiomorpholine* 1,1-*Dioxide*.—The sulphone (740 mg.) in ethanolic sodium ethoxide (12·8 ml.) was kept at 78° for 3 min. The chloroform extracts gave a product which, on treatment with ether (100 ml.), yielded unchanged sulphone (25 mg.), m. p. and mixed m. p. 200°. Evaporation of the ethereal solution gave the ethoxyethyl sulphone (820 mg.), n_D^{19} 1·5288 (infrared spectrum identical with that of an authentic specimen). No cyclic sulphone was recovered when the period of heating was extended to 20 min.

Reactions with N-5-*Chloropentylbenzamide* (IJ).—Reactions were carried out in duplicate with the chloride (2 g.) in ethanolic sodium ethoxide. Distillation gave a mixture [(i) 1·80, (ii) 1·81 g.], b. p. 140—165°/0·1 mm. Benzoic acid [(i) 0·04 g., (ii) 0·038 g.], m. p. and mixed m. p. 120—121°, was obtained from the alkaline extracts. Infrared spectroscopic analysis of the mixtures in the series X = Bz, Y = CH_2 and O is described below.

Reactions with N-5-*Iodopentylbenzamide* (IK).—Reactions were carried out in duplicate with the iodide (2 g.) in ethanolic sodium ethoxide. Distillation gave the mixture [(i) 1·355, (ii) 1·31 g.], b. p. 120—155°/0·01 mm. No benzoic acid was obtained.

N-2-2′-*Chloroethoxyethylbenzamide* (IG).—4-Benzoylmorpholine (25 g.) and phosphorus pentachloride (26·5 g.) were kept at 145° (bath) until the vigorous reaction subsided and thereafter

[16] Wieland and Mohr, *Annalen*, 1956, **599**, 222.

at 150—160° for 35 min. The cold mixture was poured on ice, and the suspension was partly neutralised (pH 4) by addition of aqueous sodium carbonate. The mixture was steam-distilled for 15 min. and the residue was extracted with ether. The extracts were washed with aqueous sodium carbonate and evaporated. The crude product (10·5 g.) had m. p. 43—47°, raised to 48° by crystallisation from ether (Found: C, 58·2; H, 6·5; N, 6·0. $C_{11}H_{14}ClNO_2$ requires C, 58·1; H, 6·2; N, 6·2%). After treatment of the chloride (2 g.) with ethanolic sodium ethoxide, acidification was omitted and extraction of the mixture with benzene gave a mixture [(i) 1·43, (ii) 1·45 g.], b. p. 125—150°/0·1 mm. Extraction of the acidified aqueous layer with methylene chloride gave benzoic acid (mean of 3 determinations, 0·210 g.), m. p. and mixed m. p. 119—120°.

Reactions with N-2-2′-*Iodoethoxyethylbenzamide* (IH).—The iodide (2 g.) and ethanolic sodium ethoxide gave, after extraction with benzene, a mixture [(i) 1·21 g., (ii) 1·19 g.], b. p. 140—160°/0·5 mm. No benzoic acid was obtained.

N-2-*Vinyloxyethylbenzamide*.—The preceding iodo-ether (14 g.) and 33% ethanolic trimethylamine (50 ml.) were kept at 20° for 48 hr. Addition of ether (200 ml.) precipitated the quaternary *iodide* (16·5 g.), m. p. 130° (sealed capillary) (from ethanol–ether) (Found: C, 44·5; H, 6·5. $C_{14}H_{23}IN_2O_2$ requires C, 44·5; H, 6·1%). The salt (16·5 g.) was vigorously stirred with silver oxide (2 mol.) in water (200 ml.) for 6 hr. Filtration of the mixture and evaporation gave the syrupy quaternary hydroxide which decomposed at 150°. After decomposition was complete, the residue was heated to 180°. The cold residue, in benzene, was washed sucessively with 0·2N-hydrochloric acid (1 l.), aqueous sodium hydrogen carbonate, and water. Evaporation of the benzene solution and distillation of the residue gave the *ether* (2·8 g.), b. p. 132°/0·3 mm., m. p. 51—52·5° (from isopropyl ether) (Found: C, 69·2; H. 6·7. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·8%).

N-2-2′-*Ethoxyethoxyethylbenzamide*.—The chloride (IG) (4·9 g.) in ethanolic sodium ethoxide (108 ml.) was refluxed for 9 hr. The mixture was poured into saturated brine and extracted with methylene chloride. Evaporation of the extracts and fractional distillation of the residue gave the *bis-ether* (1·5 g.), b. p. 143°/0·03 mm., n_D^{18} 1·5225 (Found: C, 65·9; H, 8·15; N, 5·6. $C_{13}H_{19}NO_3$ requires C, 65·9; H, 8·0; N, 5·9%). Strong bands at 1450 and 1020 cm.$^{-1}$ in the infrared spectrum of 4-benzoylmorpholine and at 1200 and 980 cm.$^{-1}$ in the infrared spectrum of the vinyl ether were absent.

Analysis of Mixtures of Products in the Series X = Bz, Y = CH_2 *and* O.—7% Chloroform solutions of each product mixture and each pure component were prepared. Aliquot parts of the solutions of the pure components were mixed so as to obtain an accurate reproduction of the infrared spectrum of the appropriate product mixture in the range 1500—850 cm.$^{-1}$. The Perkin–Elmer Infracord spectrometer was used with 0·1 mm. solution cells (NaCl windows).

TABLE 3.

Composition (%) of product mixtures.

Amide	Olefin	Cyclic	Ethoxy-compound	Amide	Olefin	Cyclic	Ethoxy-compound
IJ	6	4	90 ± 2	IG	3	23	74 ± 3
IK	28	10	62 ± 2	IH	26	31	43 ± 2

Duplicate product mixtures matched within the thickness of the trace, and the spectra of the component mixtures matched the product mixtures within 3% or better in transmission. In the series Y = CH_2, the principal bands used for matching were: olefin, 915 cm.$^{-1}$; piperidine, 855 cm.$^{-1}$; ethoxy-compound, 1110 cm.$^{-1}$. In the series Y = O the principal bands used were: olefin, 1200 and 980 cm.$^{-1}$; morpholine, 1450 and 1020 cm.$^{-1}$; ethoxy-compound, 1105 cm.$^{-1}$. The results are shown in Table 3. The infrared spectra of the product mixtures showed no bands that were absent from the spectra of the pure components.

The corresponding results given in Table 4 are corrected for benzoic acid isolated and give the yields (as % of theoretical) based on the weights of the product mixtures.

Hydrolysis of Products from Reactions in the Series Y = O.—4-Benzoylmorpholine, *N*-2-vinyloxyethylbenzamide, *N*-2-2′-ethoxyethoxyethylbenzamide were each treated with ethanolic sodium ethoxide under the standard reaction conditions for 3 hr. The yields of benzoic acid were 66, <2, and <4%, respectively. The vinyl ether (98%) was recovered, with m. p. and mixed m. p. 51—52°.

Discussion

It is probable [17] that the reactions of internal substitution (cyclisation), external substitution (by EtO^-), and elimination, which occur under the conditions employed, are either S_N2 or $E2$. The doubtful cases are the toluene-*p*-sulphonates [18] (IA), (IB), (ID), and (IP), but phenethyl toluene-*p*-sulphonates [19] show both S_N2 and $E2$ behaviour under conditions similar to those used in the present work, and the most reactive member (IA) of the series is unchanged in the absence of base. The kinetics of the reactions will be the subject of a later paper and the present discussion is based on these assumptions.

Table 4.

Products (%) obtained from reactions of amides (I) with ethanolic sodium ethoxide.

	Amide (I) (p. 3677)			Reaction time	Yield (%) of product (see Table 2)			
	X	Y	Z	(min.)	Cyclic (V)	Olefin (VI)	Ethoxy-compound (VII)	M. p. and mixed m. p.
IA	Ts	NTs	OTs	5	99	—	—	300° [a, b]
IB	Ts_2	NTs	OTs	5	93	—	—	300 [b]
IC	Ts	NTs	Cl	5	98	—	—	300 [b]
ID	Bz	NTs	OTs	5	96	—	—	167—169
IE	Bz	NTs	I	3	63	31(26 [c])	—	[a]
IF	Bz	NTs	Cl	20	69	22 [c]	—	[a]
IG	Bz	O	Cl	180	39	3	51	[a]
IH	Bz	O	I	20	31	25	35	[a]
IJ	Bz	CH_2	Cl	10 [g]	5	7	79	[a]
IK	Bz	CH_2	I	20	11	31	56	[a]
IL	BrS [h]	O	Cl	30	96	—	—	149—151 [d]
IM	BrS	O	I	30	95	—	—	151—155 [d]
IN	Ts	CH_2	Cl	5	97	—	—	95—96
IO	BrS	CH_2	Cl	3	96	—	—	85—88 [e]
IP	Ts	CH_2	OTs	3	100	—	—	98—100
IQ	Bz	S	Cl	3	—	78	3	[a]
IR	Bz	SO	Cl	2	—	—	97	88—90
IS	Bz	SO_2	Cl	1	—	—	97	106—110
IT	Ts	SO_2	Cl	1	4·5	—	88 [f]	[a]

[a] See Experimental section. [b] Lit.,[5] m. p. 291°. [c] As $Bz{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NHTs$. [d] Lit.,[20] m. p. 153—154°. [e] Lit.,[21] m. p. 89—90°. [f] Time variable. [g] Hours. [h] BrS = p-$Br{\cdot}C_6H_4{\cdot}SO_2$.

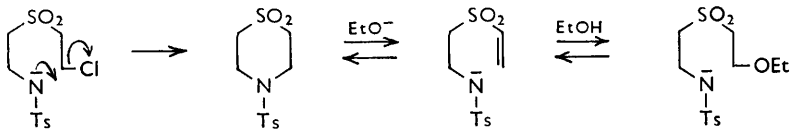
The sulphonamides (I; X = BrS or Ts) give high yields (>93%) of cyclic product irrespective of changes in structure at Y and Z. The sulphonamido-group is largely ionised under the reaction conditions (benzenesulphonamide has [22] $pK^{25}_a = 10{\cdot}0$) and consequently the high concentration of " internal " nucleophile allows cyclisation to occur with the exclusion of the external reactions of elimination and replacement. Even triethylamine causes cyclisation of (IA) in high yield. Removal of a toluene-*p*-sulphonamido-group must precede cyclisation of the amide (IB).

The sulphone (IT) is exceptional; the yield of cyclic product is dependent upon the reaction time and varies from 14% (5 sec.) to 0 (20 min.). A proportion of the sulphone initially cyclises to the thiomorpholine sulphone (V; * X = Ts, Y = SO_2) and this is subsequently cleaved in a reversible elimination–addition sequence [23] which requires the sulphonamido-nitrogen atom to be disubstituted for its operation.[24] The large excess of ethoxide ion present causes the equilibrium to be in favour of the ethoxy-sulphone (VII;

* For (V—VII) see Table 2.

[17] Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, section 25.
[18] Ref. 17, section 24d.
[19] De Puy and Bishop, *J. Amer. Chem. Soc.*, 1960, **82**, 2532.
[20] Shupe, *J. Assoc. Offic. Agric. Chemists*, 1942, **25**, 227.
[21] Marvel and Smith, *J. Amer. Chem. Soc.*, 1923, **45**, 2696.
[22] Willi, *Helv. Chim. Acta*, 1956, **39**, 46.
[23] Kader and Stirling, following paper.
[24] Stirling, *Chem. and Ind.*, 1960, 933.

X = Ts, Y = SO_2). This is confirmed by the formation of (VII) from (V) under the reaction conditions.

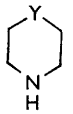
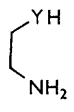


The extent of ionisation of the benzamido-compounds (I; X = Bz) is considerably lower; *N*-methylbenzamide is not detectably ionised [25] in a dilute solution of sodium isopropoxide in propan-2-ol. Competition by the external nucleophile, therefore, is expected to be more important. This is true of the series Y = CH_2, O, SO, or SO_2, and elimination also occurs when Y = CH_2, O, S, or NTs. The markedly different product distributions obtained with Y = S, SO, and SO_2, are considered to be due to fundamental mechanistic differences and these will be discussed separately.

In the three series, Y = NTs, O, and CH_2, the yields of cyclic product fall in this order irrespective of the leaving group, and for a given leaving group the extent of external substitution rises. Effects (other than steric) at the site of substitution should not greatly affect the competition between internal and external substitution. The explanation for the variation in cyclisation yield is, therefore, to be sought in the effect of the group Y on the internal nucleophile, the benzamido-group. Both the oxygen atom and the toluene-*p*-sulphonamido-group (Y = O and NTs) will inductively strengthen the acidity of the benzamido-group and hence promote cyclisation. The effects of the groups in lowering the basicity of amines [26] and raising the acidity of acids [27] (Table 5) show that the inductive

TABLE 5.

pK_a Values of acids and bases.*

	Bases [26]		Acids [27]	
				
Y				
CH_2	11·13	10·67	$CH_3{\cdot}CH_2{\cdot}CO_2H$	4·88
O	8·36	9·45	$MeO{\cdot}CH_2{\cdot}CO_2H$	3·47
TsN	7·44	9·05 †	$TsNH{\cdot}CH_2{\cdot}CO_2H$	3·46

* As conjugate acids.
† Calc.

effect decreases in the order, NTs>O>CH_2. This is the order of decreasing cyclisation and increasing replacement yields. β-Substituents with a $-I$ effect generally retard [28] S_N2 reactions of alkyl halides, while in the present work, the chloro-ether (IG) reacted faster than the chloride (IJ), supporting the conclusion that inductive strengthening of the amido-group acidity is significant. In addition, a steric effect is considered to weigh against replacement in the compounds (I; X = Bz, Y = NTs). The two strong dipoles (NTs and C=O) will cause the molecule to adopt conformations in which these dipoles are opposed. Models show two likely conformations which take into account both the steric requirements and the dipole of the leaving group. The first has the benzamido-nitrogen atom close to the rear side of the carbon atom bearing the leaving group, and in this arrangement cyclisation is favoured while replacement is difficult for steric reasons. The second conformation is linear with the benzamido-group in the *trans*-arrangement, and the carbon atom bearing the leaving group projecting from the main chain. Approach of ethoxide ion to the rear side of the carbon atom bearing the leaving group is adversely

[25] Hine and Hine, *J. Amer. Chem. Soc.*, 1952, **74**, 5266.
[26] Hall, *J. Amer. Chem. Soc.*, 1956, **78**, 2570.
[27] (*a*) Verkade, *Rec. Trav. chim.*, 1916, **35**, 91; (*b*) Palomaa, *Chem. Zentr.*, 1912, II, 596; (*c*) Loven, *Z. phys. Chem.*, 1896, **19**, 456.
[28] Tutwiler and McKee, *J. Amer. Chem. Soc.*, 1954, **76**, 6342; Akagi, Oae, and Murakami, *ibid.*, 1956 **78**, 4034; 1957, **79**, 3118.

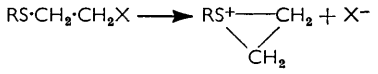
affected by the strong sulphonyl dipole and, when this effect is minimised, steric hindrance becomes serious. Removal of β-protons in elimination is relatively little affected in either conformation.

The extents of elimination in the series Y = O and CH_2 are nearly the same; at first this result was surprising in view of the expectation of increased elimination in the oxygen series caused by inductive strengthening of the acidity of the hydrogens β to the leaving group.[29] Under kinetic conditions, elimination has, however, been shown to be unimportant in the reaction of 2-fluoroethyl bromide [30] with hydroxide ion, and not to occur at all with the 2-bromoethyltrimethylammonium cation [31] and 2-methoxyethyl iodide.[32] Further, dehydrobromination of β-bromo-acetals [33] gives βγ-unsaturated acetals and not keten acetals. The failure to obtain olefin from the toluene-*p*-sulphonate (ID) accords with the previously observed [19] low reactivity of toluene-*p*-sulphonates in *E*2 reactions.

Hydrolysis at the amido-group is a complication in reactions of the chlorides (IF), (IG), and (IJ). The acyclic products from (IG) are much less rapidly hydrolysed [34] under the reaction conditions than is 4-benzoylmorpholine, and the benzoic acid obtained has been assumed to arise entirely from this source. The other chlorides yield much less benzoic acid and no differentiation between the products has been made in applying corrections to the yields given in Table 2.

The compounds with sulphur β to the leaving group present a totally different product distribution. Elimination occurs very rapidly in β-halogeno-sulphones, and the vinyl sulphones which are obtained are very susceptible to nucleophilic (Michael) addition.[35] Two-stage elimination–addition has been shown [23] to occur under similar conditions with other β-substituted sulphones and it is considered that, with compounds (IS) and (IR), elimination is the exclusive primary step. Rapid addition of ethoxide ion to the vinyl sulphone or sulphoxide ensues. 4-Benzoylthiomorpholine 1,1-dioxide was stable in the reaction conditions and, had it been formed, could have been detected. Its absence suggests that direct replacement by ethoxide ion does not occur; competition by the internal nucleophile would otherwise be expected. The failure of the internal nucleophile to compete in addition to the vinyl sulphone is not understood.

Solvolysis of β-halogeno-sulphides is known [36] to be very rapid and formation of a cyclic sulphonium salt has been suggested:



If this process occurs under the present conditions, abstraction of a proton from the sulphonium cation must take precedence over displacements by the internal and external nucleophiles. Another possibility is the encouragement of elimination in the chlorosulphide by *d*-orbital resonance stabilisation of the incipient carbanion.[37] Good yields of vinyl sulphides have frequently been obtained [38] from β-halogeno-sulphides in basic conditions.

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[29] Ref. 17, p. 446.
[30] Hine and Langford, *J. Amer. Chem. Soc.*, 1956, **78**, 5002.
[31] Doering and Schreiber, *J. Amer. Chem. Soc.*, 1955, **77**, 514.
[32] Klemperer, McCabe, and Sindler, *J. Amer. Chem. Soc.*, 1952, **68**, 3425.
[33] McElvain, Clarke, and Jones, *J. Amer. Chem. Soc.*, 1942, **64**, 1966.
[34] Cf. Johnston, *J.*, 1961, 2335.
[35] Alexander and McCombie, *J.*, 1931, 1913; Bergmann, Ginsburg, and Pappo, *Org. Reactions*, 1959, **10**, 179.
[36] Böhme and Sell, *Chem. Ber.*, 1948, **81**, 123.
[37] Cilento, *Chem. Rev.*, 1960, **60**, 147.
[38] Brown and Moggridge, *J.*, 1946, 816; Schrader, G.P. 1,089,749; Montanari, *Boll. sci. Fac. Chim. ind. Bologna*, 1956, **14**, 55.