The Schmidt Reaction with Benzocycloalkenones

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Eighteen 1-indanones, fifteen 1-tetralones, two 1-benzosuberanones, and two benzocyclobutenones, as well as four acetophenones, have been submitted to the Schmidt reaction in sulphuric acid, polyphosphoric acid, or molten trichloroacetic acid, and the ratios of the respective isomeric rearrangement products have been determined. The direction of the rearrangement in the Schmidt reaction with benzocyclobutenones and 1-indanones is strongly affected by the substituents in the aromatic ring in positions *para* or *ortho* to the carbonyl group, and by the acid medium used in the reaction. The same influence was observed to a lesser extent, but still markedly, with 1-tetralones. In ketones having a flexible structure, such as 1-benzosuberanones and acetophenones, no appreciable influence of substituents and acid mediums was noted on the direction of migration, giving in all cases predominantly *N*-aryl amide.

ALTHOUGH it has been stated [1] that the Schmidt reaction with aryl, alkyl, and cycloalkenyl ketones, including acetophenone, 1′- and 2′-acetonaphthone, and 1-tetralone, gives almost exclusively *N*-aryl amides as a result of aryl migration, we [2] have shown that alkyl migration predominates in the Schmidt reaction in sulphuric acid with 1-indanones containing a methoxy-substituent in the aromatic ring *para* or *ortho* to the carbonyl group, and a derivative of 6-methoxy-1-tetralone yields about equimolecular amounts of the aryl and the alkyl migration product. Based on these findings, it was concluded that the methoxy-group in the position *para* or *ortho* to the carbonyl group in these compounds must have played a significant role in determining the direction of migration. We have used this property to advantage in the synthesis of compounds related to alkaloids containing a 2-benzazepine moiety.[3] Recently it has been found [4] that the Schmidt reaction with 4-chromanones in sulphuric acid did not give 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones, but rather the isomeric lactams, 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones, were obtained as a result of alkyl migration due to electronic effects of the ether linkage *ortho* to the carbonyl group. These findings prompted us to investigate whether the electronic effects of a variety of substituents in an aromatic nucleus operate in the Schmidt reaction not only with 1-tetralones and 1-indanones, but also with other benzocycloalkenones.

The reaction was applied to the unsubstituted 1-indanone, 1-tetralone, 1-benzosuberanone, and benzocyclobutenone as parent benzocycloalkenones, as well as to the corresponding ketones carrying the methoxy-, hydroxy-, acetoxy-, amino-,† acetamido-, and chloro-substituents as electron-releasing groups and a nitro-substituent as an electron-attracting group. Our effort was directed mainly toward the ketones carrying *para*-substituents, thereby avoiding problems in interpretation due to the steric hindrance arising from *ortho*-substituents. *meta*-Substituents would not be expected to possess the electronic effects, but ketones carrying substituents in this position were included in the study.

First, 1-indanone (Ia) and a series of 5-substituted 1-indanones (Ib)—(Ih), in which the substituents were located in the position *para* to the carbonyl group, were submitted to the Schmidt reaction in 93% sulphuric acid, to give pairs of isomeric lactams having the carbostyril (II) and isocarbostyril (III) structure in the ratios as determined by g.l.c. (Table 1). The structures of these compounds were established principally by the n.m.r. spectra using the deuterium exchange reaction of NH protons as reported in the previous paper.[2]

It is apparent from the data in Table 1 that the presence of the electron-releasing methoxy-, hydroxy-, amino-, or chloro-group in the 5-position of 1-indanone [(Ib), (Ic), (Ie), and (Ig)] resulted in a higher ratio of alkyl migration than occurred with the parent compound (Ia). A nitro-group (Ih) in the same position resulted in a greater aryl migration than occurred in the unsubstituted ketone (Ia). Because of its electron-releasing group, 5-acetamido-1-indanone (If) was expected to give a higher ratio of alkyl migration than 1-indanone (Ia) itself, but our experiment showed that the aryl migration was greater. Attempts to study this possible anomaly with 5-acetoxy-1-indanone (Id) were unsuccessful, because the acetoxy-group was hydrolysed in the reaction medium.

Then a series of 6-substituted 1-indanones (Ii)—(Io) were treated with sodium azide in 93% sulphuric acid. As shown in Table 1, the presence of the amino-, acetamido-, chloro-, or nitro-group in the 6-position [(Il), (Im), (In), and (Io)] had a small tendency to decrease the ratio of alkyl migration as compared with the unsubstituted compound (Ia). Attempts to study the influence of the methoxy- and hydroxy-groups in the

† Under the acidic conditions of the Schmidt reaction, an amino-group is in equilibrium with a protonated form which is considered to be electron-attracting group.

[1] (*a*) H. Wolff, *Org. Reactions*, 1946, **3**, 307, and references there cited; (*b*) P. A. S. Smith, 'Molecular Rearrangements,' part I, ed. P. de Mayo, Interscience, New York, 1963, p. 457, and references there cited.

[2] S. Minami, M. Tomita, H. Takamatsu, and S. Uyeo, *Chem. and Pharm. Bull* (*Japan*), 1965, **13**, 1084.

[3] (*a*) S. Uyeo, H. Irie, A. Yoshitake, and A. Ito, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 427; (*b*) S. Uyeo, H. Shirai, A. Koshiro, T. Yashiro, and K. Kagei, *ibid.*, 1966, **14**, 1033; (*c*) N. Hazama, H. Irie, T. Mizutani, T. Shingu, M. Takada, S. Uyeo, and A. Yoshitake, *J. Chem. Soc.* (*C*), 1968, 2947; (*d*) Y. Misaka, T. Mizutani, M. Sekido, and S. Uyeo, *Chem. Comm.*, 1967, 1258; *J. Chem. Soc.* (*C*), 1968, 2954.

[4] (*a*) D. Huckle, I. M. Lockhart, and M. Wright, *J. Chem. Soc.*, 1965, 1137; (*b*) D. Evans and I. M. Lockhart, *ibid.*, p. 4806.

6-position [(Ii) and (Ij)] resulted in concomitant sulphonation, at least in part, and the use of g.l.c. to determine the ratio of aryl and alkyl migration was prevented. However, since we have ascertained that sulphonation takes place only with lactams of the carbostyril type, we can assume that the chloroform-insoluble sulphonic acid is derived from a product resulting from aryl migration. 6-Methoxy-1-indanone (Ii) gave a chloroform-soluble fraction and a chloroform-insoluble sulphonic acid. The ratio of the components of the chloroform-soluble fraction was estimated by g.l.c., and the approximate migration ratio was calculated by taking account of the amount of the sulphonic acid (IVi) as mentioned in Table 1. The reaction of 6-hydroxy-1-indanone (Ij) gave similarly a chloroform-soluble fraction and a chloroform-insoluble sulphonic acid (IVj). The chloroform-soluble fraction consisted of the lactam (IIj) and a trace of starting material, none of the isomeric lactam (IIIj) being detected by g.l.c. It was presumed, therefore, that the migration in this case is almost exclusively of the aryl type. 6-Acetoxy-1-indanone (Ik) was hydrolysed readily by 93% sulphuric acid, followed by the same type of migration as observed with 6-hydroxy-1-indanone. The foregoing results indicated that substituents *para* to the carbonyl group in 1-indanones play an important role in determining the ratio of direction of migration in the Schmidt reaction in 93% sulphuric acid, while *meta*-substituents were without any significant effects, as expected.

Next, 1-tetralone (Va) and a series of the 6- and 7-substituted 1-tetralones (Vb)—(Vo) were subjected to the Schmidt reaction using 93% sulphuric acid as a reaction medium. As shown in Table 1, of 1-tetralones possessing an electron-releasing group at 6-position, only 6-methoxy- and 6-hydroxy-1-tetralone (Vb) and (Vc) showed more alkyl migration than 1-tetralone (Va). On the other hand, the migration ratio of alkyl group with 6-amino-1-tetralone (Ve) was the same as that of 1-tetralone (Va), while that with 6-acetamido-, 6-chloro-, and 6-nitro-1-tetralone (Vf)—(Vh) was less. 6-Acetoxy-1-tetralone (Vd) gave the same result as did 6-hydroxy-1-tetralone owing to hydrolysis in sulphuric acid, followed by rearrangement. Of the 1-tetralones having an electron-releasing or -attracting substituent at the 7-position, 7-amino-, 7-acetamido-, and 7-nitro-1-tetralone, (Vl), (Vm), and (Vo), showed a little higher aryl migration than did 1-tetralone itself, and the result with 7-chloro-1-tetralone (Vn) was the same as that with 1-tetralone (Va). The migration ratios in the Schmidt reaction with 7-methoxy- and 7-hydroxy-1-tetralone (Vi) and (Vj) were determined as described for 6-methoxy-1-indanone (Ii), because simultaneous sulphonation occurred, and were found to be about the same as that for 1-tetralone itself. 7-Acetoxy-1-tetralone (Vk) underwent hydrolysis in the Schmidt reaction in sulphuric acid. These findings suggested that, in contrast to 5-substituted 1-indanones, only very strongly electron-releasing substituents, *viz.*, the methoxy- and hydroxy-groups at the 6-position of 1-tetralones, showed a preference for alkyl migration in the Schmidt reaction in 93% sulphuric acid, while the electronic effects of a variety of substituents at the 7-position of 1-tetralones were inappreciable.

In this connection, it may be added that the concentration of sulphuric acid in the Schmidt reaction did not affect the ratio of migration products, as shown with 1-indanone, 5-methoxy-1-indanone, 1-tetralone, and 6-methoxy-1-tetralone, though the yields of the mixture of the rearrangement products were far lower in 76% sulphuric acid than in 93% acid, and about the same in 98% acid as in 93% acid under otherwise the same conditions. When the Schmidt reaction on 1-indanones and 1-tetralones was carried out in polyphosphoric acid

TABLE 1

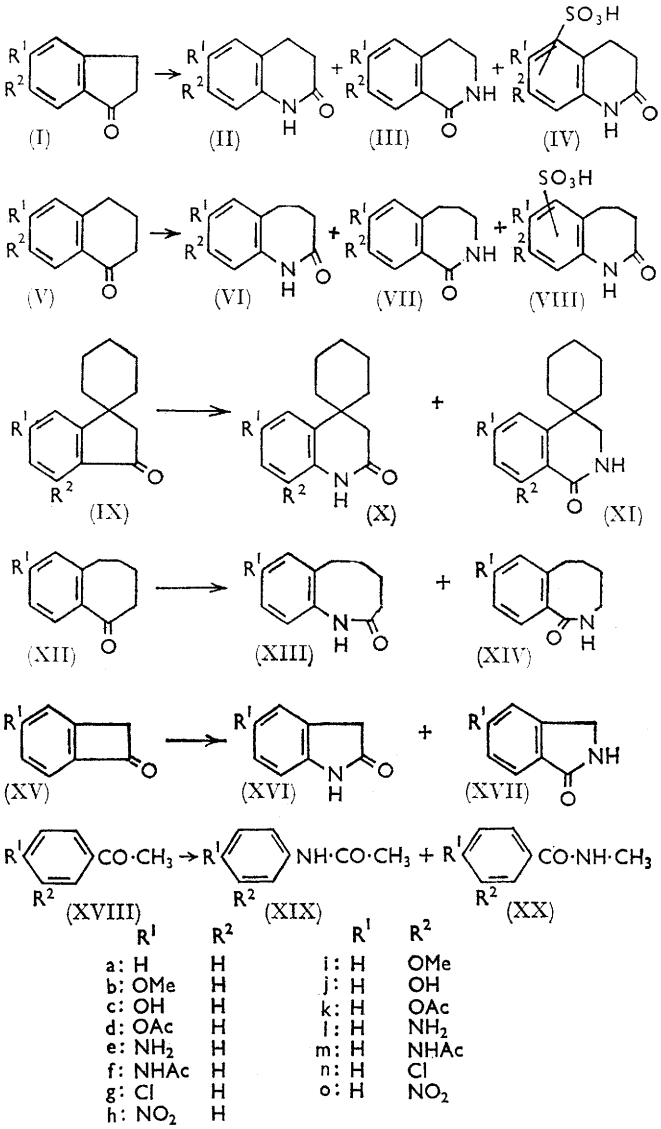
Alkyl migration ratios * in the Schmidt reactions with various ketones as determined by g.l.c.

Compd.	Acid	Alkyl migration ratio (%) 10	20	30	40	50	60	70	80	90
(XV)	93% H_2SO_4			a						b
	$Cl_3C{\cdot}CO_2H$									b
(I)	98% H_2SO_4				a					b
	93% H_2SO_4	f, h, j, l, m	n, o	a, i †	g		e		c	b
	76% H_2SO_4				a					b
	Polyphosphoric acid			a						b
	$Cl_3C{\cdot}CO_2H$								a, d, h, i, k, n, o	b, c, e, f, g, j, m
(IX)	93% H_2SO_4			a						b, i
	$Cl_3C{\cdot}CO_2H$								a	b, i
(V)	98% H_2SO_4		a				b			
	93% H_2SO_4	f, g, h, l, m, o	a, e, i,† j,† n		c		b			
	76% H_2SO_4	a					b			
	Polyphosphoric acid	a						b		
	$Cl_3C{\cdot}CO_2H$	o	e, h	a, d, i, j, k, m, n	g, l		b, c, f			
(XII)	93% H_2SO_4		a, b							
	$Cl_3C{\cdot}CO_2H$		a, b							
(XVIII)	93% H_2SO_4	a, h, o	b							
	$Cl_3C{\cdot}CO_2H$	a, h, o	b							

* The relative ratios of the yields of alkyl migration products are based on the amounts of mixtures of migration products.
† An approximate value estimated by the method mentioned in the text owing to sulphonation of a migration product.

instead of 93% sulphuric acid, the yields were somewhat lower, but the ratios of the respective migration products were very similar to those obtained in 93% sulphuric acid.

In comparison with the above results, the Schmidt reaction in molten trichloroacetic acid is noteworthy (Table 1). Although the reaction rate in this acid is slower than in 93% sulphuric acid, the predominant products with the derivatives of 1-indanone, irrespective of the type and position of substituents, involve the compounds resulting from alkyl migration. In the cases of the derivatives of 1-tetralone, the migration ratios of the alkyl group are not so remarkable as those of 1-indanones, but it is certain that in almost all cases the ratios of the alkyl migration were increased in the



	R^1	R^2		R^1	R^2
a:	H	H	i:	H	OMe
b:	OMe	H	j:	H	OH
c:	OH	H	k:	H	OAc
d:	OAc	H	l:	H	NH_2
e:	NH_2	H	m:	H	NHAc
f:	NHAc	H	n:	H	Cl
g:	Cl	H	o:	H	NO_2
h:	NO_2	H			

reaction in trichloroacetic acid than in sulphuric acid or polyphosphoric acid. The reason for this trichloroacetic acid reversal of the yields obtained using sulphuric acid or polyphosphoric acid is not clear.

Considering the fact that both the electronic effects of substituents and the effects of trichloroacetic acid operate more strongly in the Schmidt reaction with five-membered 1-indanones than six-membered 1-tetralones, it is presumed that both effects relate to the conformation of the ketones. Therefore, the direction of migration in the Schmidt reaction with 1-benzosuberanones (XII), possessing a more flexible seven-membered structure than 1-tetralones, will be little influenced by the electronic and trichloroacetic acid effects. In contrast, in the case of benzocyclobutenones (XV), having a more rigid four-membered structure than 1-indanones, the situation will be reversed. To confirm this assumption, 1-benzosuberanone (XIIa) and its 7-methoxy-derivative (XIIb) were first subjected to the reaction using 93% sulphuric acid and molten trichloroacetic acid, respectively. Since the reaction with these two seven-membered compounds (XIIa) and (XIIb) proceeded in the same migration ratio (Table 1) regardless of the substituents and acids, neither the electronic nor the trichloroacetic acid effects are operative in the reaction with the seven-membered ring compounds.

The Schmidt reaction was then applied to benzocyclobutenone (XVa) and its 4-methoxy-derivative (XVb) in sulphuric acid, although these compounds were rather unstable in this medium and considerable amounts of starting materials were decomposed under the reaction conditions. As shown in Table 1, the principal type of rearrangement from benzocyclobutenone (XVa) involved aryl migration, while that of the 4-methoxy-derivative (XVb) involved alkyl migration. It is apparent, therefore, that the methoxy-group in the 4-position has the electronic effects to give alkyl migration as we expected. In trichloroacetic acid the reaction with the 4-methoxy-compound (XVb) proceeded to give the alkyl migration product as shown in Table 1; however, no migration was observed with the parent ketone (XVa). Therefore, the effects of trichloroacetic acid could not be evaluated in this case.

In order to obtain further information on the relation between the trichloroacetic acid effects and the structure of the ketones, certain non-cyclic ketones such as acetophenones were submitted to the Schmidt reaction in trichloroacetic acid and compared with the results obtained by the reaction in 93% sulphuric acid. As recorded in Table 1, acetophenones (XVIIIa), (XVIIIb), (XVIIIh), and (XVIIIo) gave invariably acetanilides (XIXa), (XIXb), (XIXh), and (XIXo) rather than the isomeric benzamides (XXa), (XXb), (XXh), and (XXo) regardless of the substituents in the ring and of acids used. Therefore, trichloroacetic acid is considered to have no effect in changing the course of this reaction in these cases.

In view of the above facts, the most reasonable conclusion to be drawn is that the ratio of the directions of migration in the Schmidt reaction with benzocycloalkenones possessing a rigid and nearly plane structure is affected by the electronic effects of the substituents in the aromatic ring in the position *para* or *ortho* to the

carbonyl group and by the effects of trichloroacetic acid, to cause in certain cases predominant alkyl migration to occur, while with the increase of flexibility of the alicyclic ring in ketones, the electronic effects of substituents in the aromatic ring and the effects of the reaction medium decrease, resulting in the increase of the ratio of aryl migration to be close to that in the cases with acetophenones. We are not yet able to predict the course of the reaction in quantitative terms.

EXPERIMENTAL

Infrared spectra were measured on a type EPI-S_2 Hitachi recording spectrophotometer, and n.m.r. spectra on a Varian A-60 spectrometer with deuteriochloroform or deuteriopyridine as solvent and tetramethylsilane as internal reference. Gas–liquid chromatography was carried out using a Barber Colman model 10 instrument.

Preparation of the Starting Materials.—With the exception of the new compounds, 5-nitroindanone, 6-acetoxyindanone, 6-nitrotetralone, and 4-methoxybenzocyclobutenone, all other ketones used for the Schmidt reaction were prepared by the methods described in the literature.

(a) *5-Nitroindanone* (Ih). Sodium nitrite (30 g.) was slowly added with stirring to a cooled solution of 5-aminoindanone (3·0 g.) in 1·6% nitric acid (150 ml.) and cuprocuprisulphite (7·2 g.) was added. After vigorous evolution of nitrogen had ceased, the solution was warmed on a steam-bath for 20 min. and extracted with chloroform; the extracts were washed with water, dried, and evaporated to dryness, to give the *product* (Ih). Recrystallisation from ether gave pale orange prisms (0·72 g.), m.p. 128—130° (Found: C, 61·4; H, 4·2; N, 7·9. $C_9H_7NO_3$ requires C, 61·0; H, 4·0; N, 7·9%).

(b) *6-Acetoxyindanone* (Ik). 6-Hydroxyindanone was acetylated with acetic anhydride in pyridine to give the *product* (Ik) (90%), m.p. 122—124° (from acetone) (Found: C, 69·6; H, 5·4. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%).

(c) *6-Nitrotetralone* (Vh). In the same manner as described above, 6-aminotetralone was converted into the *product* (36%). It crystallised from n-hexane as pale orange needles, m.p. 111—113° (Found: C, 62·8; H, 5·0; N, 7·2. $C_{10}H_9NO_3$ requires C, 62·8; H, 4·8; N, 7·3%).

(d) *4-Methoxybenzocyclobutenone* (XVb). A mixture of 3-bromo-4-methoxybenzocyclobutenone [5] (3·9 g.) and zinc dust (7·8 g.) in water (80 ml.) was stirred at 90° for 12 hr. and filtered. The filtrate was extracted with ether, and the extract was dried and concentrated to dryness, to give the *product* (2·5 g.). Recrystallisation from n-hexane gave prisms, m.p. 44—45° (Found: C, 72·7; H, 5·4. $C_9H_8O_2$ requires C, 73·0; H, 5·4%), $\nu_{max.}$ (KBr) 1758sh and 1744 cm.$^{-1}$, τ ($CDCl_3$) 6·11 (OCH_3) and 6·13 (CH_2). The *2,4-dinitrophenylhydrazone* formed orange crystals from ethyl acetate, m.p. 245—247° (Found: C, 55·1; H, 3·7; N, 16·9. $C_{15}H_{12}N_4O_5$ requires C, 54·9; H, 3·7; N, 17·1%).

General Procedures for the Schmidt Reaction.—(a) *In sulphuric acid.* To a mixture of a ketone (0·01 mole) in benzene (0·2 mole) and sulphuric acid (0·1 mole) was added sodium azide (0·01 mole) with stirring at 60—64°, and stirring was continued for several minutes. The mixture was cooled in an ice-bath, and the benzene layer was separated by decantation and discarded. The acid layer was diluted with ice–water, neutralised with sodium hydrogen carbonate if necessary, and extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness, to give a crude product which was analysed by g.l.c. The remaining portion of the product was purified by chromatography over silica gel or alumina, and crystallised from a suitable solvent to give pure compounds. In the case of 5-hydroxyindanone (Ic), whose rearrangement products were very soluble in water, neutralised aqueous layer was concentrated to dryness under reduced pressure, and the residue was extracted with acetone to give a mixture of products which was analysed by g.l.c.

In the case of Schmidt reactions on (Ii), (Ij), (Vi), and (Vj), in which simultaneous sulphonation took place, the reaction mixture was diluted with a small amount of ice–water to separate the sulphonated lactams, (IVi), (IVj), (VIIIi), and (VIIIj) respectively, as crystals which were filtered and washed well with acetone. These compounds were identical with respective samples which were synthesised alternatively as described below. The filtrate was extracted with chloroform and the extract was analysed by g.l.c. The m.p.s and analytical values are summarised in Table 2.

(b) *In polyphosphoric acid.* Each ketone (0·01 mole) was dissolved in 12—16 parts of polyphosphoric acid, and the theoretical amount of sodium azide was added with stirring at 60—64°. The whole was stirred for about 15 min., cooled, and diluted with ice–water. After neutralisation with sodium hydrogen carbonate, the mixture was extracted with chloroform, which was dried, concentrated to dryness, and analysed by g.l.c.

(c) *In trichloroacetic acid.* The theoretical amount of sodium azide was added to a mixture of a ketone (0·01 mole) and molten trichloroacetic acid (0·1 mole) at 62—65°, and stirring was continued for several hours. The solution was then cooled, diluted with ice–water, neutralised with sodium hydrogen carbonate, and extracted with chloroform, dried, concentrated to dryness, and analysed by g.l.c. Purification of the product was performed as mentioned above. In the Schmidt reaction with those having a hydroxy- or acetoxy-group, the diluted aqueous phase was extracted directly with chloroform without neutralisation, and the extract was dried and evaporated to dryness, to afford an oil which was washed with ether and then with n-hexane to remove trichloroacetic acid, and analysed by g.l.c. Isolation of the individual products was performed by chromatography followed by crystallisation.

Sulphonation of the Lactams (IIi), (IIj), (VIi), and (VIj).—The respective lactams (0·5 g.) were treated with 93% sulphuric acid (1·5 ml.) at 100° for 2 min., cooled, and diluted with ice–water (1·5 ml.), to give the corresponding sulphonated lactams (IVi), (IVj), (VIIIi), and (VIIIj) in 75—80% yields, respectively, which were collected on a filter and washed with acetone. Six-membered lactams were purified by reprecipitation from their saturated aqueous solutions by acetone. Attempts to purify the seven-membered lactams by recrystallisation from water were unsuccessful owing to hydrolysis of the lactam moiety of the compounds to give the respective *amino-acids*: m.p. 193—194°, from (VIIIi) (Found: C, 45·4; H, 5·5; N, 4·5; S, 10·8. $C_{11}H_{15}NO_6S$ requires C, 45·7; H, 5·2; N, 4·8; S, 11·1%); m.p. 263—265° (decomp.), from (VIIIj) (Found: C, 43·7; H, 4·9; N, 5·1; S, 11·6. $C_{10}H_{13}NO_6S$ requires C, 43·6; H, 4·8; N, 5·1; S, 11·7%).

[5] (*a*) A. J. Birch, J. M. Brown, and F. Stansfield, *J. Chem. Soc.*, 1964, 5343; (*b*) G. M. Iskander and F. Stansfield, *J. Chem. Soc.*, 1965, 1390.

TABLE 2

Lactams obtained by the Schmidt reaction and by alternative synthesis

Compound	M.p.	Recryst. from [a]	Found (%) C	H	N	S	Formula	Required (%) C	H	N	S
(IIa)	162—163° [b]	A	73·1	6·1	9·5		C_9H_9NO	73·5	6·2	9·5	
(IIe)	174—175 [c]	B	67·1	6·3	16·9		$C_9H_{10}N_2O$	66·7	6·2	17·3	
(IIf)	259—261 [c]	C	64·3	5·8	13·8		$C_{11}H_{12}N_2O_2$	64·7	5·9	13·7	
(IIg)	165—166 [d]	B	59·8	4·6	7·5		C_9H_8ClNO	59·5	4·4	7·7	
(IIh)	202—203 [c]	B	56·0	4·1	14·4		$C_9H_8N_2O_3$	56·3	4·2	14·6	
(IIi)	145—146 [e]	B	67·6	6·4	8·1		$C_{10}H_{11}NO_2$	67·8	6·3	7·9	
(IIj)	228—230 [e]	A	66·4	5·7	8·7		$C_9H_9NO_2$	66·2	5·6	8·6	
(IIk)	155—157	D	64·4	5·4	7·0		$C_{11}H_{11}NO_3$	64·4	5·4	6·8	
(IIl)	211—212 [f]	A	66·3	6·2	17·3		$C_9H_{10}N_2O$	66·7	6·2	17·3	
(IIm)	288—289 [g]	C	64·9	6·0	13·2		$C_{11}H_{12}N_2O_2$	64·7	5·9	13·7	
(IIn)	189—190 [h]	B	59·5	4·6	7·5		C_9H_8ClNO	59·5	4·4	7·7	
(IIo)	242—243 [i]	B	56·7	4·1	14·4		$C_9H_8N_2O_3$	56·3	4·2	14·6	
(IIIa)	150/4 mm. [j] (bath temp.)		73·4	6·4	9·0		C_9H_9NO	73·5	6·2	9·5	
(IIIb)	139—140 [k]	B	68·0	6·3	8·1		$C_{10}H_{11}NO_2$	67·8	6·3	7·9	
(IIIc)	223—224	A	66·1	5·8	8·4		$C_9H_9NO_2$	66·2	5·6	8·6	
(IIId)	142—143	B—D	64·3	5·5	7·1		$C_{11}H_{11}NO_3$	64·4	5·4	6·8	
(IIIe)	171—172	B	66·9	6·5	17·0		$C_9H_{10}N_2O$	66·7	6·2	17·3	
(IIIf)	198—200	B	64·5	6·0	13·8		$C_{11}H_{12}N_2O_2$	64·7	5·9	13·7	
(IIIg)	152—153	B	59·5	4·5	7·5		C_9H_8ClNO	59·5	4·4	7·7	
(IIIh)	225—228	A	56·9	4·3	14·2		$C_9H_8N_2O_3$	56·3	4·2	14·6	
(IIIi)	112—113 [l]	B	67·7	6·0	8·0		$C_{10}H_{11}NO_2$	67·8	6·3	7·9	
(IIIj)	200—202	B	66·4	5·7	8·6		$C_9H_9NO_2$	66·2	5·6	8·6	
(IIIk)	140—141	B—D	64·5	5·4	6·7		$C_{11}H_{11}NO_3$	64·4	5·4	6·8	
(IIIm)	250—251	A	64·5	6·2	13·5		$C_{11}H_{12}N_2O_2$	64·7	5·9	13·7	
(IIIn)	151—152	A	59·6	4·7	7·4		C_9H_8ClNO	59·5	4·4	7·7	
(IIIo)	216—218	B	56·1	4·2	14·3		$C_9H_8N_2O_3$	56·3	4·2	14·6	
(IVi)	260—261 [g]	B—E	46·4	4·5	5·2	12·4	$C_{10}H_{11}NO_5S$	46·7	4·3	5·4	12·5
(IVj)	285—288 [g]	B—E	44·7	3·9	5·6	13·5	$C_9H_9NO_5S$	44·4	3·7	5·8	13·2
(VIa)	139—140 [m]	A	74·7	6·7	8·8		$C_{10}H_{11}NO$	74·5	6·9	8·7	
(VIb)	141—142	A	69·0	7·0	7·6		$C_{11}H_{13}NO_2$	69·1	6·9	7·3	
(VIc)	244—245	C	67·7	6·3	8·1		$C_{10}H_{11}NO_2$	67·8	6·3	7·9	
(VId)	140—141	B—D	65·8	6·2	6·2		$C_{12}H_{13}NO_3$	65·7	6·0	6·4	
(VIe)	186—187	A	68·0	6·9	16·0		$C_{10}H_{12}N_2O$	68·2	6·9	15·9	
(VIf)	242—243	A	65·9	6·6	12·9		$C_{12}H_{14}N_2O_2$	66·0	6·5	12·8	
(VIg)	164—165	F	60·9	5·2	7·1		$C_{10}H_{10}ClNO$	61·4	5·2	7·2	
(VIh)	225—227 [n]	B	58·4	5·0	13·7		$C_{10}H_{10}N_2O_3$	58·3	4·9	13·6	
(VIi)	132—134 [o]	B	69·0	6·7	7·4		$C_{11}H_{13}NO_2$	69·1	6·9	7·3	
(VIj)	227—228 [p]	B—C	67·8	6·4	8·0		$C_{10}H_{11}NO_2$	67·8	6·3	7·9	
(VIk)	121—122	D—G	66·0	6·1	6·1		$C_{12}H_{13}NO_3$	65·7	6·0	6·4	
(VIl)	229—231 [g]	C	67·9	6·8	15·9		$C_{10}H_{12}N_2O$	68·2	6·9	15·9	
(VIm)	216—217	B	65·9	6·4	12·8		$C_{12}H_{14}N_2O_2$	66·0	6·5	12·8	
(VIn)	157—158	B	61·7	5·4	7·0		$C_{10}H_{10}ClNO$	61·4	5·2	7·2	
(VIo)	223—224 [p]	C	58·5	4·9	13·8		$C_{10}H_{10}N_2O_3$	58·3	4·9	13·6	
(VIIb)	160—161 [q]	A	69·0	6·9	7·3		$C_{11}H_{13}NO_2$	69·1	6·9	7·3	
(VIIc)	238—239	C	67·6	6·2	7·8		$C_{10}H_{11}NO_2$	67·8	6·3	7·9	
(VIId)	131—132	B—D	65·7	6·2	6·5		$C_{12}H_{13}NO_3$	65·7	6·0	6·4	
(VIIe)	165—166	B	68·0	6·8	15·9		$C_{10}H_{12}N_2O$	68·2	6·9	15·9	
(VIIf)	192—193	B	65·8	6·5	12·9		$C_{12}H_{14}N_2O_2$	66·0	6·5	12·8	
(VIIg)	183—184	B	61·7	5·5	7·1		$C_{10}H_{10}ClNO$	61·4	5·2	7·2	
(VIIi)	100—101	D	69·1	6·7	7·2		$C_{11}H_{13}NO_2$	69·1	6·9	7·3	
(VIIk)	120—121	D	65·7	6·1	6·1		$C_{12}H_{13}NO_3$	65·7	6·0	6·4	
(VIIm)	240—241	B	65·7	6·2	13·0		$C_{12}H_{14}N_2O_2$	66·0	6·5	12·8	
(VIIn)	160—161	B	61·6	5·1	6·9		$C_{10}H_{10}ClNO$	61·4	5·2	7·2	
(VIIIi)	230—232 [g]		46·7	4·8	5·0	11·8	$C_{11}H_{13}NO_5S,\frac{1}{2}H_2O$	47·1	5·0	5·0	11·4
(VIIIj)	274—275 [g]		45·1	4·2	5·4	12·9	$C_{10}H_{11}NO_5S,\frac{1}{2}H_2O$	45·1	4·5	5·3	12·0
(XIIIa)	150—151 [r]	A—D	75·6	7·6	8·2		$C_{11}H_{13}NO$	75·4	7·5	8·0	
(XIIIb)	145—146	D	70·2	7·3	7·0		$C_{12}H_{15}NO_2$	70·2	7·4	6·8	
(XVIa)	122—123 [s]	A—G	72·1	5·4	10·6		C_8H_7NO	72·2	5·3	10·5	
(XVIb)	149—151 [t]	B	66·3	5·8	8·9		$C_9H_9NO_2$	66·2	5·6	8·6	
(XVIIa)	151—152 [u]	A—E	72·5	5·3	10·4		C_8H_7NO	72·2	5·3	10·5	
(XVIIb)	161—162 [v]	A	66·0	5·6	9·0		$C_9H_9NO_2$	66·2	5·6	8·6	

[a] Solvents for recrystallisation were (A) ethanol, (B) acetone, (C) methanol, (D) ether, (E) water, (F) chloroform, (G) n-hexane. [b] Lit. m.p. 163° (P. Friedlaender and A. Weinberg, *Ber.*, 1882, **15**, 1421). [c] Lit. m.p. 178° for (IIe), 263—264° for (IIf), and 203—204° for (IIh) [H. Uyeda, *Proc. Imp. Acad.* (*Tokyo*), 1939, **15**, 148]. [d] Lit. m.p. 167—168° (F. Mayer, L. van Zuetphen, and H. Philipps, *Ber.*, 1927, **60**, 858). [e] (IIi) was prepared by methylation of (IIj). Lit. m.p. 146—148° for (IIi) and 228—230° for (IIj) [N. Shigematsu, *Chem. and Pharm. Bull.* (*Japan*), 1961, **9**, 970]. [f] Lit. m.p. 211° (S. Garbriel and J. Zimmermann, *Ber.*, 1879, **12**, 600). [g] Decomposition. [h] Lit. m.p. 191° (J. Mirek, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1961, **9**, 315). [i] Lit. m.p. 247° (Z. H. Yang, *J. Taiwan Pharm. Assoc.*, 1952, **4**, 18). [j] This was obtained as an oil and was identical with an authentic sample (oil) prepared by the method of E. Bamberger and W. Dieckmann (*Ber.*, 1893, **26**, 1205), who reported m.p. 70—71° and b.p. >300°. P. T. Lansbury, J. G. Colson, and N. R. Mancuso (*J. Amer. Chem. Soc.*, 1964, **86**, 5225) obtained this lactam as an oil. [k] Lit. m.p. 139° [A. Brossi, J. Wuersch, and O. Schnider, *Chimia* (*Switz.*), 1958, **12**, 114]. [l] Lit. m.p. 112—114° (M. Tomita, S. Matsumura, Y. Sasaki, and E. Kinoshita, *J. Pharm. Soc. Japan*, 1959, **79**, 329). [m] Lit. m.p. 141° (L. H. Briggs and G. C. De Ath, *J. Chem. Soc.*, 1937, 456). [n] Lit. m.p. 220—222·5° (P. A. S. Smith and W. L. Berry, *J. Org. Chem.*, 1961, **26**, 27). [o] Lit. m.p. 131—132° (S. Nizamuddin and D. N. Chaudhury, *J. Indian Chem. Soc.*, 1963, **40**, 960). [p] Lit. m.p. 232—234° for (VIj) and 220—222° for (VIo) [lit., see in (VIh)]. [q] Lit. m.p. 115—116°. This m.p. is for a mixture of this compound and some of the isomeric 2,3,4,5-tetrahydro-7-methoxy-1*H*-1-benzazepin-2-one as stated in ref. 4*b*. [r] Lit. m.p. 151·5—153° (R. Huisgen, *Annalen*, 1951, **574**, 171). [s] Lit. m.p. 127° (R. Stollé, *J. prakt. Chem.*, 1930 [2], **128**, 1). N.m.r. spectrum: singlet at τ 6·41 (CH_2). [t] Prepared according to T. Wieland and O. Unger (*Chem. Ber.*, 1963, **96**, 253). Lit. m.p. 153°. N.m.r. spectrum: singlet at τ 6·48 (CH_2). An attempt to prepare this compound by the route reported by E. Giovanniti and P. Portmann (*Helv. Chim. Acta*, 1948, **31**, 1381) was unsuccessful. [u] Prepared according to H. Rupe and F. Bernstein (*Helv. Chim. Acta*, 1930, **13**, 457). Lit. m.p. 150°. N.m.r. spectrum: singlet at τ 5·51 (CH_2). [v] N.m.r. spectrum: singlet at τ 5·58 (CH_2).

Preparation of 5-Methoxyphthalimidine (XVIIb).—(i) *2-Cyano-4-methoxytoluene.* 2-Cyano-4-hydroxytoluene [6] (12·5 g.) was methylated with dimethyl sulphate (14 g.) and 10% aqueous sodium hydroxide (50 ml.), to give the *product* (10·5 g.), b.p. 117—118°/15 mm., m.p. 26·5—27° (Found: C, 73·7; H, 6·2; N, 9·5. C_9H_9NO requires C, 73·5; H, 6·2; N, 9·5%).

(ii) *2-Cyano-4-methoxybenzoic acid.* Oxidation of 2-cyano-4-methoxytoluene (1·35 g.) with potassium permanganate (8·4 g.) in water (50 ml.) at 68° gave the *product* (1·3 g.) as colourless needles, m.p. 214—215° (from acetone) (Found: C, 61·3; H, 4·1; N, 7·9. $C_9H_7NO_3$ requires C, 61·0; H, 4·0; N, 7·9%).

(iii) *Methyl 2-cyano-4-methoxybenzoate.* Methylation of the acid (0·7 g.) with an excess of diazomethane in methanol–ether gave the *product* quantitatively, needles from n-hexane, m.p. 87—89° (Found: C, 63·0; H, 5·0; N, 7·3. $C_{10}H_9NO_3$ requires C, 62·8; H, 4·8; N, 7·3%).

(iv) *5-Methoxyphthalimidine* (XVIIb). The methyl ester (0·5 g.) was hydrogenated over Raney nickel in methanol (30 ml.) at room temperature and atmospheric pressure for 6 hr., to give the *product* (XVIIb) (0·3 g.), m.p. 160—161° (from ethanol), which was identical with the lactam obtained by the Schmidt reaction on (XVb) as shown by mixed m.p. and comparison of the i.r. spectra.

Preparation of the Authentic Samples of Non-cyclic Amides.—These compounds were prepared by the Schotten–Baumann reaction of appropriate amines with carboxylic acid chloride according to the literature, respectively, and the identities of all these amides were confirmed by the elemental analysis as well as their m.p.s.

Determination of the Relative Ratio of the Rearrangement Products of the Schmidt Reaction by Gas–Liquid Chromatography.—The relative amount of a pair of isomeric amides in the reaction mixture was determined by g.l.c. The peak-height ratios of the chromatograms were compared with those of the calibration curves. For the cyclic amides, calibration curves, which were plotted for all the pairs of pure compounds listed in Table 2, were superimposable within experimental error, and therefore the relative ratio of migration could be estimated using this calibration curve even when the pairs of pure compounds were not obtained. For the non-cyclic amides, the calibration curves of each pair of compounds were different from each other, and accordingly the relative ratio of migration had to be estimated using independent calibration curves for respective compounds. As the column packings, QF-1 was used in all cases except for *p*-methoxyacetophenone where Carbowax 20 M was employed.

We thank Drs. W. I. Taylor (International Flavors and Fragrances, Inc., New Jersey, U.S.A.), Y. Inubushi, and H. Irie (this Department) for valuable discussions.

[8/966 *Received, July 9th,* 1968]

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