Preparation of Tetrahydroindolizines from Pyridinium and Isoquinolinium Ylides

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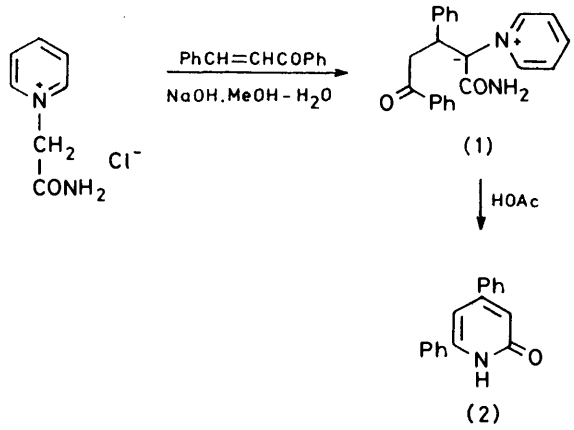
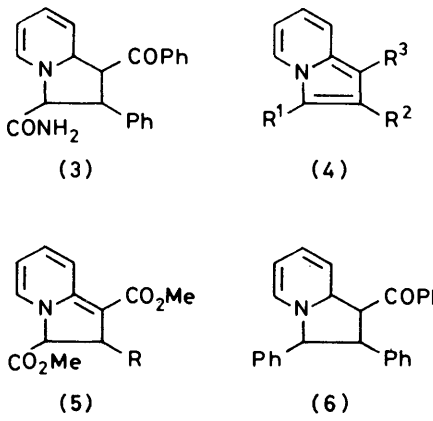
Carbonyl- and nitrile-stabilised pyridinium and cyclic azonium methylides condense with chalcones to form tetrahydroindolizines and analogous fused pyrrolidines. The stereochemistry is illuminated by ^{13}C and ^{1}H n.m.r. spectroscopy. Several incorrect literature structures are rectified.

REQUIRING efficient routes to substituted 2-pyridones,[1] we were drawn to Thesing's [2] synthesis of 4,6-diphenyl-2-pyridone (2) (Scheme 1). Pyridinium carbamoylmethylide, generated *in situ* by treatment of the salt with base, was condensed with chalcone to give an intermediate, reported [2] to have the structure (1), which was isolated and then cyclised in acid to the pyridone (2).



SCHEME 1

We obtained the same yellow intermediate, m.p. 147—148 °C (lit.,[2] m.p. 147—148 °C). However, the n.m.r. spectrum excluded the ylide formulation (1) and strongly indicated the tetrahydroindolizine structure (3), as did the i.r. spectrum (see later discussion of spectra).



The tetrahydroindolizine (3) is formed by a 1,3-dipolar cycloaddition [3] of the pyridinium ylide: there are many examples of such reactions with olefinic and acetylenic dipolarophiles in the literature,[4-8] although it is usual for the primary adducts to undergo dehydrogenation to indolizines under the reaction conditions. Thus, Boekelheide and Fahrenholz [4] treated pyridinium phenacylide with dimethyl acetylenedicarboxylate to give the indolizine (4; R^1 = PhCO, R^2 = R^3 = CO_2Me). A wide range of other ylides and alkynes have given analogous products of type (4) (*e.g.* ref. 5). Adducts from olefinic dipolarophiles frequently undergo loss of two hydrogens; thus, dihydroindolizines (5) result [6] from pyridinium methoxycarbonylide with substituted acrylates. Pyridinium, quinolinium, and isoquinolinium phenacylides and acrylonitrile give isolable but readily dehydrogenated tetrahydroindolizines.[7] Recently, Kröhnke has reported [8] stable tetrahydroindolizines (6) from the reaction of pyridinium benzylide with chalcone, and similar adducts from isoquinolinium benzylide and fluorenylides of both heterocycles.

We have now investigated the reaction of several other carbonyl-, and nitrile-stabilised cyclic azonium methylides with chalcones. The cyclic azonium salts (7a—h) and (8a—g) (Table 1) were prepared by reaction of pyridine, picolines, isoquinoline, quinoline, and benzothiazole with active halogen compounds (chloroacetamide, ethyl bromoacetate, methyl chloroacetate, chloroacetonitrile, and phenacyl chloride). The cyclic *N*-(alkoxycarbonylmethyl)azonium salts (7a), (7b), (7d), and (8a) reacted with αβ-unsaturated ketones to give the cycloadducts (9a—f), (10), (12a), and (13a–h) (Table 2). The pyridinium salt with chalcone and analogues rapidly deposits adducts (9a—f) and (10) in high yields, but of the analogous picolinium salts (7d—f) only the chalcone adduct (12a) of the 2-picolinium salts (7d) could be isolated. The corresponding isoquinolinium salts give adducts (13a—h) in moderate to high yield with αβ-unsaturated ketones, including benzalacetone. The quinolinium salt (8e) was, however, inactive. The cyclic *N*-(carbamoylmethyl)azonium salts (7c), (7g—h), and (8b) reacted with αβ-unsaturated ketones to give the adducts (11a—e), (12b and c), and (14a—e) (Table 3). The pyridinium and isoquinolinium salts (7c) and (8b) each react with chalcones in high yield. The 2- and 4-picolinium salts (7g and h) reacted more sluggishly with chalcones to give reduced yields of the crude adducts (12b and c) which resisted purification and could not be satisfactorily characterised. The quinolinium and benzothiazolium salts (8f and g) again gave no adducts.

The cyanomethylisoquinolinium salts (8c) reacted

Table 1

N-Substituted cyclic azonium salts

Salt	Heterocycle	Active halogen compound	Procedure	Yield (%)	Cryst. form	M.p. (°C)	Lit. m.p. (°C)	Lit. ref.	Found C	Found H	Found N	Found Hal	Formula	Required C	Required H	Required N	Required Hal
(7a)	Pyridine	$BrCH_2CO_2Et$	(a)	92	Prisms	135—137	135—136	*a*									
(7b)	Pyridine	$ClCH_2CO_2Me$	(b)	85	Plates	178—180 (decomp.)	191	*b*	51.5	5.3	7.3	18.9	$C_9H_{10}ClNO_2$	51.2	5.4	7.5	18.9
(7c)	Pyridine	$ClCH_2CONH_2$	(c)	95	Prisms	207—209	202—203	*c*									
(7i)	[$^2H_5$]Pyridine	$ClCH_2CO_2Me$	(b)	90	Prisms	180			50.3		7.3	18.4	$C_8H_4{}^2H_6ClNO_2$	49.9		7.3	18.4
(7j)	[$^2H_5$]Pyridine	$ClCH_2CONH_2$	(c)	95	Prisms	217—219			47.4		15.6	20.0	$C_7H_4{}^2H_2ClN_2O$	47.3		15.8	20.0
(7d)	2-Picoline	$BrCH_2CO_2Et$	(a)	75	Prisms	127—128	128	*d*									
(7g)	2-Picoline	$ClCH_2CONH_2$	(c)	95	Prisms	216—218			51.6	5.8	15.1	19.0	$C_8H_{11}ClN_2O$	51.5	5.9	15.0	19.0
(7e)	3-Picoline	$BrCH_2CO_2Et$	(a)	88	Prisms	154—156			46.1	5.3	5.4	30.8	$C_{10}H_{14}BrNO_2$	46.2	5.4	5.4	30.8
(7f)	4-Picoline	$BrCH_2CO_2Et$	(a)	95	Plates	163—165			46.5	5.4	5.2	31.2	$C_{10}H_{14}BrNO_2$	46.2	5.4	5.4	30.8
(7h)	4-Picoline	$ClCH_2CONH_2$	(c)	98	Prisms	230—232			51.5	6.0	15.0	19.1	$C_8H_{11}ClN_2O$	51.5	5.9	15.0	19.0
(8a)	Isoquinoline	$BrCH_2CO_2Et$	(a)	95	Prisms	199	199	*e*									
(8b)	Isoquinoline	$ClCH_2CONH_2$	(c)	62	Prisms	235—236			59.0	5.2	12.5	16.0	$C_{11}H_{11}ClN_2O$	59.3	4.9	12.6	15.9
(8c)	Isoquinoline	$ClCH_2CN$	(d)	68	Prisms	214			64.5	4.4	13.6	17.4	$C_{11}H_7ClN_2$	64.5	4.4	13.7	17.3
(8d)	Isoquinoline	$BrCH_2COPh$	(a)	98	Prisms	204	204—206	*f*									
(8e)	Quinoline	$BrCH_2CO_2Et$	(a)	76	Prisms	180	180	*g*									
(8f)	Quinoline	$ClCH_2CONH_2$	(c)	40	Prisms	228—230			59.0	5.0	12.4	15.7	$C_{11}H_{11}ClN_2O$	59.3	4.9	12.6	15.9
(8g)	Benzothiazole	$ClCH_2CONH_2$	(c)	58	Prisms	220—222			47.3	3.9	12.1	15.5	$C_9H_7ClN_2OS$	47.3	4.0	12.3	15.5

a F. Kröhnke, *Ber.*, 1937, **70**, 543. *b* N. N. Mel'nikov, N. D. Sukhareva, and O. P. Arkhipova, *Zh. Prikl. Khim.*, 1947, **20**, 642—8 (*Chem. Abs.*, 1949, **43**, 6976h). *c* A. H. Cook, J. Downer, and B. Hornung, *J. Chem. Soc.*, 1941, 502. *d* O. Westphal, K. Jann, and W. Heffe, *Arch. Pharm.* (*Weinheim, Ger.*), 1961, **294**, 37. *e* H. Ihlder, *Arch. Pharm.* (*Weinheim, Ger.*), 1902, **240**, 505. *f* F. Kröhnke, *Ber.*, 1935, **68**, 1177. *g* H. Ihlder, *Arch. Pharm.* (*Weinheim, Ger.*), 1902, **240**, 517—518.

Table 2

Adducts from cyclic *N*-(ethoxycarbonylmethyl)azonium salts *a*

Adduct	Heterocycle	αβ-Unsaturated ketone $Ar^1COCH{=}CH{\cdot}Ar^2$ Ar^1	Ar^2	Yield (%)	Cryst. solvent	Cryst. form	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
(9a)	Pyridine	Ph	Ph	90	EtOH	Yellow needles	104—105	77.0	6.5	3.7	$C_{24}H_{21}NO_3$	77.2	6.2	3.8
(9b)	Pyridine	Ph	*p*-ClC_6H_4	93	EtOH–H_2O	Yellow microcrystals	118—120	70.9	5.3	3.3	$C_{24}H_{20}ClNO_3$ *b*	70.7	5.4	3.4
(9c)	Pyridine	Ph	*p*-MeC_6H_4	66	EtOH	Yellow needles	105—106	77.6	6.7	3.4	$C_{25}H_{23}NO_3$	77.5	6.5	3.6
(9d)	Pyridine	2-F *c*	Ph	72	EtOH	Yellow prisms	94—96	69.2	6.1	3.6	$C_{22}H_{21}NO_4{\cdot}H_2O$ *d*	69.3	6.1	3.7
(9e)	Pyridine	*p*-ClC_6H_4	*p*-ClC_6H_4	80	EtOH	Yellow prisms	93—95	65.0	4.7	3.0	$C_{24}H_{21}Cl_2NO_3$ *e*	65.1	4.8	3.2
(9f)	Pyridine	*p*-MeC_6H_4	*p*-MeC_6H_4	87	EtOH–H_2O	Yellow microcrystals	97—99 (decomp.)	77.8	6.8	3.4	$C_{26}H_{27}NO_3$	77.8	6.8	3.5
(10)	Pyridine *f*	Ph	Ph	90	MeOH	Yellow needles	91—92	76.8	5.7	3.8	$C_{23}H_{21}NO_3$	76.9	5.9	3.9
(12a)	2-Picoline	Ph	Ph	70	EtOH	Yellow needles	103—104	77.1	6.4	3.5	$C_{25}H_{23}NO_3$	77.5	6.5	3.6
(13a)	Isoquinoline	Me	Ph	75	Me_2CO–H_2O	Yellow prisms	120	76.4	6.4	3.7	$C_{23}H_{23}NO_3$	76.4	6.4	3.9
(13b)	Isoquinoline	Ph	Ph	65	EtOAc	Yellow needles	138	79.2	5.9	3.3	$C_{28}H_{25}NO_3$	79.4	6.0	3.3
(13c)	Isoquinoline	Ph	*p*-$MeOC_6H_4$	78	Me_2CO–H_2O	Yellow prisms	109	76.5	5.9	3.0	$C_{29}H_{27}NO_4$	76.8	6.0	3.1
(13d)	Isoquinoline	Ph	*p*-$NO_2C_6H_4$	55	Me_2CO–H_2O	Yellow prisms	136	71.8	5.0	5.9	$C_{28}H_{24}N_2O_5$	71.8	5.2	6.0
(13e)	Isoquinoline	Ph	2-F *c*	44	Me_2CO–H_2O	Yellow prisms	114	76.0	5.7	3.3	$C_{28}H_{22}NO_4$	75.5	5.6	3.4
(13f)	Isoquinoline	2-T *g*	Ph	87	Me_2CO–H_2O	Yellow prisms	138	72.8	5.4	3.2	$C_{26}H_{21}NO_3S$ *h*	72.7	5.4	3.3
(13g)	Isoquinoline	*p*-ClC_6H_4	*p*-ClC_6H_4	33	Me_2CO–H_2O	Yellow prisms	128	68.4	4.8	2.8	$C_{28}H_{21}Cl_2NO_3$ *i*	68.3	4.7	2.8
(13h)	Isoquinoline	*p*-MeC_6H_4	*p*-MeC_6H_4	67	EtOH	Yellow plates	139	79.6	6.4	3.0	$C_{30}H_{29}NO_3$	79.8	6.5	3.1
(16a)	[$^2H_5$]Pyridine *f*	Ph	Ph	90	MeOH	Yellow needles	87—88	75.7		3.8	$C_{23}H_{16}{}^2H_5NO_3$	75.8		3.8

a Prepared by general method (a). *b* Found: Cl, 8.8. Required: Cl, 8.7%. *c* 2-F = 2-Furyl. *d* Hygroscopic, H_2O seen in spectra. *e* Found: Cl, 16.3. Required: Cl, 16.0%. *f* Methoxycarbonymethyl salt. *g* 2-T = 2-Thienyl. *h* Found: S, 7.6. Required: S, 7.5%. *i* Found: Cl, 14.5. Required: Cl, 14.4%.

Table 3

Adducts from cyclic 1-(carbamoylmethyl)azonium salts *a*

Adduct	Heterocycle	αβ-Unsaturated ketone $R^1COCH{=}CHR^2$ R^1	R^2	Yield (%)	Cryst. solvent	Cryst. form	M.p. (°C)	Found C	H	N	Formula	Required C	H	N
(11a)	Pyridine	Ph	Ph	90	MeOH–H_2O	Yellow prisms	147—148 *b*	76.4	6.1	8.1	$C_{23}H_{20}N_2O_2$	76.7	5.9	8.1
(11b)	Pyridine	Ph	*p*-ClC_6H_4	74	EtOH	Yellow prisms	145—146	69.6	5.0	7.3	$C_{23}H_{19}ClN_2O_2$ *c*	69.7	5.1	7.4
(11c)	Pyridine	2-Furyl	Ph	70	EtOH	Yellow prisms	139—140			8.0	$C_{20}H_{16}N_2O_3$			8.4
(11d)	Pyridine	*p*-ClC_6H_4	*p*-ClC_6H_4	70	EtOH	Yellow plates	146—147	64.1	4.4	6.7	$C_{23}H_{18}Cl_2N_2O_2$ *d*	63.9	4.4	6.8
(11e)	Pyridine	*p*-MeC_6H_4	*p*-MeC_6H_4	86	EtOH	Yellow plates	146—147	77.4	6.6	7.5	$C_{25}H_{24}N_2O_2$	77.4	6.5	7.5
(14a)	Isoquinoline	Ph	Ph	90	EtOH–H_2O	Yellow microcrystals	110—112	79.1	5.6	6.6	$C_{26}H_{22}N_2O_2$	79.2	5.6	7.1
(14b)	Isoquinoline	Ph	*p*-ClC_6H_4	90	EtOH	Flat yellow needles	151—152.5	71.0	5.7	5.9	$C_{26}H_{21}ClN_2O_2{\cdot}$ EtOH *e*	70.8	5.7	5.9
(14c)	Isoquinoline	2-Furyl	Ph	90	EtOH	Yellow needles	186—187			6.9	$C_{24}H_{20}N_2O_3$			7.3
(14d)	Isoquinoline	*p*-ClC_6H_4	*p*-ClC_6H_4	90	EtOH	Yellow needles	165—167	67.1	4.3	6.0	$C_{26}H_{20}Cl_2N_2O_2$ *f*	67.4	4.4	6.0
(14e)	Isoquinoline	*p*-MeC_6H_4	*p*-MeC_6H_4	90	MeOH–H_2O	Yellow microcrystals	105—108	79.0	6.2		$C_{28}H_{26}N_2O_2{\cdot}$ $\frac{1}{2}H_2O$ *g*	78.8	6.3	
(16b)	[$^2H_5$]Pyridine	Ph	Ph	90	MeOH–H_2O	Yellow prisms	155—157	75.6		7.9	$C_{23}H_{15}{}^2H_5N_2O_2$	75.6		8.0

a Prepared by general method (b). *b* Lit., m.p. 147—148 °C (ref. 2). *c* Found: Cl, 9.3. Required: Cl, 9.4%. *d* Found: Cl, 17.2. Required: Cl, 17.2%. *e* Spectra show EtOH. Found: Cl, 7.6. Required: Cl, 7.5%. *f* Found: Cl, 15.3. Required: Cl, 15.3%. *g* Hygroscopic.

Table 4

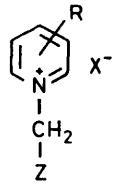
Adducts from 1-(cyanomethyl)isoquinolinium salts *a*

Adduct	αβ-Unsaturated ketone $R^1COCH{=}CHR^2$ R^1	R^2	Yield %	Cryst. form *b*	M.p. (°C)	Found C	H	N	Formula	Required C	H	N
(15a)	Me	Ph	4	White microcrystals	165	77.8	5.5	8.7	$C_{21}H_{16}N_2O$	80.2	5.8	8.9
(15b)	Bu^t	Ph	34	White needles	147	81.0	6.8	7.9	$C_{24}H_{24}N_2O$	80.9	6.8	7.9
(15c)	Ph	Ph	42	Yellow micro-crystals	184—185			7.4	$C_{26}H_{20}N_2O$			7.4
(15d)	Ph	*p*-$MeOC_6H_4$	47	Yellow plates	67	79.8	5.3	6.9	$C_{27}H_{22}N_2O_2$	79.8	5.5	6.9
(15e)	Ph	*p*-$NO_2C_6H_4$	52	Yellow needles	190	74.1	4.4		$C_{26}H_{19}N_3O_3$	74.1	4.5	

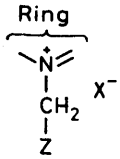
a Prepared by general method (c). *b* From EtOH.

with αβ-unsaturated ketones to give the adducts (15a—e) in moderate to low yield (Table 4). Salts (7i and j) were formed by reaction of pentadeuteriated pyridine with methyl chloroacetate and with chloroacetamide. Reactions of these salts with chalcone gave the expected adducts (16a and b), in which the deuterium label was fully retained.

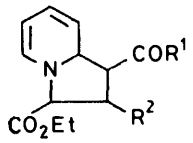
Spectra of the Tetrahydroindolizines.—The i.r. and n.m.r. spectra of the adducts (9a—f), (10), (11a—e), (12a), and (16a and b) derived from pyridinium salts are



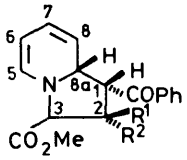
(7) a; R = H, Z = CO_2Et, X = Br
b; R = H, Z = CO_2Me, X = Cl
c; R = H, Z = $CONH_2$, X = Cl
d; R = 2-Me, Z = CO_2Et, X = Br
e; R = 3-Me, Z = CO_2Et, X = Br
f; R = 4-Me, Z = CO_2Et, X = Br
g; R = 2-Me, Z = $CONH_2$, X = Cl
h; R = 4-Me, Z = $CONH_2$, X = Cl
i; R = 2,3,4,5,6-penta-^{2}H, Z = CO_2Me, X = Cl
j; R = 2,3,4,5,6-penta-^{2}H, Z = $CONH_2$, X = Cl



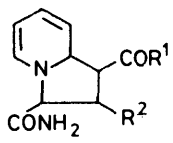
(8) a; Ring = isoquinolinium, Z = CO_2Et, X = Br
b; Ring = isoquinolinium, Z = $CONH_2$, X = Cl
c; Ring = isoquinolinium, Z = CN, X = Cl
d; Ring = isoquinolinium, Z = COPh, X = Br
e; Ring = quinolinium, Z = CO_2Et, X = Br
f; Ring = quinolinium, Z = $CONH_2$, X = Cl
g; Ring = benzothiazolium, Z = $CONH_2$, X = Cl



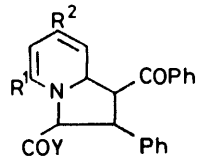
(9) a; $R^1 = R^2 = Ph$
b; $R^1 = Ph$, $R^2 = p$-ClC_6H_4
c; $R^1 = Ph$, $R^2 = p$-MeC_6H_4
d; $R^1 = 2$-Furyl, $R^2 = Ph$
e; $R^1 = R^2 = p$-ClC_6H_4
f; $R^1 = R^2 = p$-MeC_6H_4



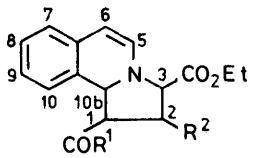
(10) a; $R^1 = H$, $R^2 = Ph$
b; $R^1 = Ph$, $R^2 = H$



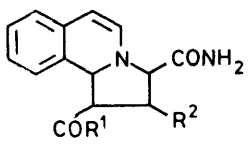
(11) a; $R^1 = R^2 = Ph$
b; $R^1 = Ph$, $R^2 = p$-ClC_6H_4
c; $R^1 = 2$-Furyl, $R^2 = Ph$
d; $R^1 = R^2 = p$-ClC_6H_4
e; $R^1 = R^2 = p$-MeC_6H_4



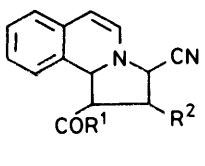
(12) a; $R^1 = Me$, $R^2 = H$, Y = OEt
b; $R^1 = Me$, $R^2 = H$, $Y = NH_2$
c; $R^1 = H$, $R^2 = Me$, $Y = NH_2$



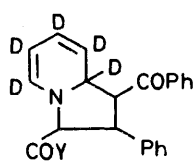
(13) a; $R^1 = Me$, $R^2 = Ph$
b; $R^1 = R^2 = Ph$
c; $R^1 = Ph$, $R^2 = p$-$MeOC_6H_4$
d; $R^1 = Ph$, $R^2 = p$-$NO_2C_6H_4$
e; $R^1 = Ph$, $R^2 = 2$-Furyl
f; $R^1 = 2$-Thienyl, $R^2 = Ph$
g; $R^1 = R^2 = p$-ClC_6H_4
h; $R^1 = R^2 = p$-MeC_6H_4



(14) a; $R^1 = R^2 = Ph$
b; $R^1 = Ph$, $R^2 = p$-ClC_6H_4
c; $R^1 = 2$-Furyl, $R^2 = Ph$
d; $R^1 = R^2 = p$-ClC_6H_4
e; $R^1 = R^2 = p$-MeC_6H_4



(15) a; $R^1 = Me$, $R^2 = Ph$
b; $R^1 = Bu^t$, $R^2 = Ph$
c; $R^1 = R^2 = Ph$
d; $R^1 = Ph$, $R^2 = p$-$MeOC_6H_4$
e; $R^1 = Ph$, $R^2 = p$-$NO_2C_6H_4$



(16) a; Y = OMe
b; $Y = NH_2$

TABLE 5

I.r. and ^{1}H n.m.r. spectra of adducts (8) derived from pyridinium salts

Adduct	X	R	R^1	ν(C=O)	ν(C=C)	1-H	2-H	3-H	5-H	6-H	7-H	8-H	8a-H	Aromatic	OCH$_3$	OCH$_3$	ArCH$_3$	Other CH$_3$	Coupling constants $J_{1,2}$	$J_{1,8a}$	$J_{2,3}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,8a}$
(9a)	CO_2Et	Ph	Ph	1 735 *a*	1 675	1 640	4.54 *b,c*	3.92 *d*	4.23 *e,f*	6.10 *g*	4.75 *h,i*	5.88 *j*	4.97 *f,h*	4.85 *h,i*	7.1—7.8 *h,q*	4.23 *f,r*			1.25 *e*	9	9	6	7	5.5	9.5	3
(9b)	CO_2Et	Ph	*p*-ClC_6H_4	1 735 *a*	1 675	1 630	4.48 *b,c*	3.92 *d*	4.15 *e,f*	6.09 *g*	4.75 *h,i*	5.87 *j*	4.97 *f,h*	4.85 *h,i*	7.1—7.8 *h,s*	4.22 *f,r*			1.28 *e*	8.5	8.5	6.5	7	5.5	9.5	*i*
(9c)	CO_2Et	Ph	*p*-MeC_6H_4	1 730 *k*	1 665	1 635	4.55 *b,c*	3.91 *d*	4.19 *e,f*	6.08 *g*	4.75 *h,i*	5.85 *j*	4.95 *f,h*	4.85 *h,i*	7.0—7.9 *h,s*	4.19 *f,r*		2.24 *t*	1.25 *e*	9	9	6.5	7	5.5	9	*i*
(9d)	CO_2Et	2-F	Ph	1 730 *a*	1 650	1 610	4.29 *b,e,f*	3.91 *d*	4.20 *e,f*	6.09 *g*	4.75 *h,i*	5.88 *j*	5.03 *h*	4.85 *h,i*	6.9—7.6 *h,u*	4.20 *f,r*			1.25 *e*	9	9	6	7	5.5	9.5	3
(9e)	CO_2Et	*p*-ClC_6H_4	*p*-ClC_6H_4	1 730 *a*	1 675	1 625	4.41 *b,c*	3.89 *d*	4.14 *e,f*	6.09 *g*	4.8 *h,i*	5.89 *j*	4.94 *h*	4.8 *h,i*	7.1—7.8 *h,u*	4.22 *f,r*			1.28 *e*	8.5	8.5	6	7	5.5	9	*i*
(9f)	CO_2Et	*p*-MeC_6H_4	*p*-MeC_6H_4	1 735 *a*	1 670	1 610	4.52 *b,e*	3.92 *d*	4.19 *e,f*	6.08 *g*	4.75 *h,i*	5.84 *j*	4.95 *f,h*	4.84 *h,i*	6.95—7.8 *h,u*	4.21 *r*		2.31, *t* 2.24 *t*	1.26 *e*	9	9	6	7	5.5	9	*i*
(12a)	CO_2Et *m*	Ph	Ph	1 740 *a*	1 670	1 640	4.43 *b,c*	3.88 *d*	4.24 *e,f*		4.57 *h,i*	5.81 *j*	5.01 *h*	4.86 *h,i*	7.1—7.8 *h,q*	4.24 *f,r*		1.80 *t*	1.28 *e*	8.5	9	6		5.5	9.5	3
(10)	CO_2Me	Ph	Ph	1 740 *n*	1 670	1 630	4.55 *b,e*	3.94 *d*	4.25 *e*	6.10 *g*	4.79 *d,f*	5.89 *j*	5.00 *h*	4.83 *d,f*	7.2—7.8 *h,q*		3.79 *t*			9	9	6	7	5.5	9.5	3
(16a)	CO_2Me *o*	Ph	Ph	1 740 *a*	1 670	1 600	4.53 *b,e*	3.92 *d*	4.23 *e*						7.1—7.8 *h,q*		3.73 *t*			9		6				
(16b)	$CONH_2$ *o*	Ph	Ph	1 680 *a*	1 665	1 600	4.58 *e,p*	3.81 *d*	4.18 *e*						7.1—7.8 *h,q*					9		7				
(11a)	$CONH_2$	Ph	Ph	1 680 *n*	1 660	1 590	4.7 *i,p*	3.88 *d*	4.21 *e*	6.27 *g*	4.7 *h,i*	5.86 *j*	4.91 *h*	4.75 *h,i*	7.1—7.9 *h,q*					9	*i*	7	7	5.5	10	3
(11b)	$CONH_2$	Ph	*p*-ClC_6H_4	1 680 *a*	1 660	1 640	4.7 *i,p*	3.84 *d*	4.19 *e*	6.24 *g*	4.7 *h,i*	5.87 *j*	4.90 *h*	4.75 *h,i*	7.1—7.9 *h,s*					9	*i*	7	7	5.5	10	3
(11c)	$CONH_2$	2-F	Ph	1 685 *a*	1 640	1 600	4.40 *d,p*	3.78 *d*	4.11 *e*	6.18 *g*	4.6 *h,i*	5.85 *j*	4.90 *h*	4.7 *h,i*	7.0—8.0 *h,u*					8	9	7	7	5.5	10	3
(11d)	$CONH_2$	*p*-ClC_6H_4	*p*-ClC_6H_4	1 695 *k*	1 650	1 590	4.65 *i,p*	3.84 *d*	4.17 *e*	6.24 *g*	4.65 *h,i*	5.87 *j*	4.92 *h*	4.7 *h,i*	7.1—8.0 *h,u*					8	*i*	7	7	5.5	9.5	3
(11e)	$CONH_2$	*p*-MeC_6H_4	*p*-MeC_6H_4	1 700 *a*	1 650	1 610	4.65 *i,p*	3.84 *d*	4.16 *e*	6.22	4.65 *h,i*	5.85 *j*	4.90 *h*	4.7 *h,i*	7.0—7.7 *h,u*			2.29, 2.20		8	*i*	7	7	5.5	10	3

a In Nujol. *b* In $CDCl_3$. *c* Triplet. *d* Double doublet. *e* Doublet. *f* Signals overlap. *g* Doublet of triplets. *h* Multiplet. *i* Not distinguishable due to overlap. *j* Double doublet of triplets. *k* In $CHBr_3$. *l* 2-F = 2-Furyl. *m* From the 2-picolinium salt. *n* As a KBr disc. *o* Pentadeuteriated adduct. *p* In $(CD_3)_2SO$. *q* 10 H. *r* Quartet. *s* 9 H. *t* Singlet. *u* 8 H.

TABLE 6

I.r. and ^{1}H n.m.r. spectra of adducts (9) derived from isoquinolinium salts

Adduct	X	R	R^1	ν(C=O)	ν(C=C)	1-H	2-H	3-H [a]	5-H [a]	6-H [a]	10b-H [a]	Aromatic	Others (2 H)	Methyl groups	$J_{1,2}$	$J_{1,10b}$	$J_{2,3}$	$J_{5,6}$
(13a)	CO_2Et	Me	Ph	1 740 [b] 1 715	1 620	4.05 [c,d]	3.85 d	4.32	6.28	5.58	5.00	6.7—7.4 [n,o]	3.68 [p]	2.12,[q] 0.88 [d]	8.5	8.5	9	7
(13b)	CO_2Et	Ph	Ph	1 735 [b] 1 665	1 630	4.72 [c,d]	3.87 [d]	4.37	6.45	5.63	5.20	6.8—7.8 [n,f]	3.70 [d]	0.80 [d]	8.5	9	9	7.5
(13c)	CO_2Et	Ph	p-$MeOC_6H_4$	1 750 [b] 1 680	1 615	4.69 [c,d]	3.85 [d]	4.35	6.45	5.62	5.19	6.6—7.9 [n,s]	3.75 [d]	3.72,[q] 0.86 [d]	8	9	9	7
(13d)	CO_2Et	Ph	p-$NO_2C_6H_4$	1 733 [b] 1 665	1 630	4.68 [c,d]	3.94 d	4.42	6.48	5.68	5.20	6.8—8.5 [n,s]	3.80 [p]	0.84 [d]	7	9	9	8
(13e)	CO_2Et	Ph	2-F [f]	1 740 [b] 1 665	1 615	5.00 [d,g]	4.15 [d]	4.40	6.27	5.55	5.29	6.0—7.9 [n,t]	3.95 [p]	1.00 [d]	8.5	9	9	7
(13f)	CO_2Et	2-T [h]	Ph	1 745 [b] 1 650	1 615	4.55 [c,d]	3.94 [d]	4.38	6.40	5.62	5.24	6.6—7.7 [n,t]	3.70 [p]	0.78 [d]	8.5	9	9	7
(13g)	CO_2Et	p-ClC_6H_4	p-ClC_6H_4	1 732 [b] 1 670	1 630	4.58 [c,d]	3.82 [i]	4.34	6.44	5.64	5.16	6.7—7.75 [n,t]	3.75 [p]	0.86 [d]	8.5	8.5	9	7.5
(13h)	CO_2Et	p-MeC_6H_4	p-MeC_6H_4	1 755 [b] 1 670	1 615	4.71 [c,d]	3.87 [d]	4.36	6.44	5.62	5.21	6.6—7.75 [n,t]	3.72 [p]	2.24,[q] 2.35,[q] 0.82 [d]	8	8.5	9	7.5
(14a)	$CONH_2$	Ph	Ph	1 680 [j]	1 610	4.74 [c,d]	3.92 [d]	4.18	6.32	5.65	5.14	6.6—7.8 [n,p]	6.20 [q]		9	8.5	9.5	7
(14b)	$CONH_2$	Ph	p-ClC_6H_4	1 680 [b] 1 670	1 630	4.67 [c,d]	3.93 [d]	4.17	6.35	5.73	5.12	6.55—7.85 [n,s]	6.04 [q]		9	8.5	9.5	7.5
(14c)	$CONH_2$	2-F [f]	Ph	1 665 [j] 1 655	1 615	4.78 [c,d]	3.99 [d]	4.32	6.37	5.48	5.08	6.6—7.8 [n,t]	6.6—7.8 [i]		9	9	9	7.5
(14d)	$CONH_2$	p-ClC_6H_4	p-ClC_6H_4	1 690 [b] 1 670	1 630	4.62 [d,g]	3.92 [d]	4.24	6.40	5.46	5.01	6.6—7.9 [n,t]			10	10	9.5	7.5
(14e)	$CONH_2$	p-MeC_6H_4	p-MeC_6H_4	1 670 [j]	1 610	4.72 [c,d]	3.96 [d]	4.22	6.34	5.67	5.12	6.6—7.9 [n,t]	6.00 [q]	2.32,[q] 2.20 [q]	9	9	9.5	7
(15a)	CN	Me	Ph	1 705 [b,k]	1 630	4.08 [c,e]	3.72 [e]	4.84	6.07	5.38	5.55	7.1—7.4 [n,o]		1.75 [q]	6	8.5	8	7.5
(15b)	CN	But	Ph	1 690 [b,k]	1 625	4.13 [e,g]	3.53 [e]	4.67	6.53	5.67	4.77	6.8—7.4 [n,o]		0.71 [o,g]	7.5	9.3	8.5	7.5
(15c)	CN	Ph	Ph	1 670 [b,k]	1 630	4.64 [d,l]	3.81 [d]	4.60	6.45	5.68	5.10	7.0—7.6 [n,s]			8	8.5	8	7.5
(15d)	CN	Ph	p-$MeOC_6H_4$	1 620 [b,k]	1 615	4.70 [c,d]	3.84 [b]	4.62	6.46	5.72	5.17	6.6—7.8 [n,s]		3.76 [q]	8.5	8.5	8.5	7.5
(15e)	CN	Ph	p-NO_2Ph	1 670 [b,k]	1 630	[m]												
(17)	COPh	Ph	Ph	1 680 [b] 1 670	1 615	4.66 [c,e]	3.92 [e]	5.23	6.46	5.68	5.34	6.7—7.8 [n,u]			7	8	8	7

[a] Doublet. [b] In $CHBr_3$. [c] In $CDCl_3$. [d] Triplet. [e] Double doublet. [f] 2-F = 2-Furyl. [g] In $(CD_3)_2SO$–$CDCl_3$. [h] 2-T = 2-Thienyl. [i] Obscured by overlapping signals. [j] In Nujol. [k] ν(C≡N) 2 250 cm^{-1}. [l] In CCl_4. [m] Insufficiently soluble to record. [n] Multiplet. [o] 9 H. [p] Quartet. [q] Singlet. [r] 14 H. [s] 13 H. [t] 12 H. [u] 19 H.

given in Table 5, and of those (13a—h), (14a—e), and (15a—e) from isoquinolinium salts in Table 6. All adducts (9)—(16) had a strong ketone ν(C=O) 1 640—1 715 cm^{-1}: the methyl ketones gave rise to highest values of ν(C=O), and the highly conjugated furyl and thienyl ketones to the lowest. The ester adducts (9a—e), (10), (12a), and (13a—h) had also an ester ν(C=O) 1 735—1 750 cm^{-1}, whilst the amides (11a—e) and (14a—e) had an amide ν(C=O) 1 660—1 680 and variable ν(NH_2) 3 100—3 500 cm^{-1}, and the nitrile adducts (15a—e) had ν(C≡N) 2 250 cm^{-1}.

The ^{1}H n.m.r. spectra of the adducts (9)—(12) from pyridinium salts were assigned on the basis of the 220 MHz spectrum of the methyl ester adduct with chalcone (10). The phenyl protons gave a 8 H multiplet at δ 7.2—7.6 and a 2 H doublet at δ 7.81, whilst the CO_2Me gave a 3 H singlet at δ 3.79. 3-H and 5-H, each having only one CH neighbour, gave doublets, all other protons giving double doublets. Deshielding by N caused 5-H and 7-H to appear at lowest field, δ 6.10 and 5.89. The signals from 6-H and 8a-H overlapped, but were distinguishable. The olefinic coupling constants $J_{5,6}$, $J_{6,7}$, $J_{7,8}$, respectively 7, 5.5, and 9.5 Hz, are normal values. Long range coupling, $J_{5,7} \approx J_{5,8} \approx J_{6,8} \approx J_{6,8a} \approx 1$ Hz, caused the signals of 5,7,8-H to be split into fine triplets, and those of 6,8a-H into fine doublets. The small $J_{8,8a}$ (3 Hz) is a consequence of the constraint of 8a-H away from the plane of the diene.

Although the large $J_{1,2}$ (9 Hz) could indicate structure (10a) in which 1-H is *cis* to 2-H, it is more likely that the phenyl and phenacyl substituents of the dipolarophile remain *trans* to each other in the adduct as in structure (10b). In (10b), steric repulsions between the phenyl groups probably keep the dihedral angle of the protons 1-H and 2-H near 180°, giving rise to a large vicinal coupling.

The off-resonance ^{13}C n.m.r. spectrum of (10) provided additional confirmation of the tetrahydroindolizine structure. The ketone and ester carbonyls gave singlets at δ 197.9 and 172.1 respectively, the quaternary aromatic carbons appeared as singlets at δ 141.1 and 137.4, and the remaining aromatic carbons as a series of doublets between δ 133.3 and 127.3 p.p.m. The olefinic carbons C-5, C-7, C-8, and C-6 appeared respectively as doublets at δ 135.2, 124.1, 115.0, and 95.7, whilst the aliphatic carbons C-8a, C-3, C-1, and C-2 gave higher field doublets at δ 72.8, 64.7, 62.4, and 49.7, and the methyl carbon resonated as a quartet at δ 52.4 p.p.m. The pentadeuteriated adduct (16a) gave a ^{1}H n.m.r. spectrum which contained only the aromatic and methyl signals, plus 3-H (a 6 Hz doublet), 1-H (a 9 Hz doublet), and 2-H (a 6 and 9 Hz double doublet), thus confirming the assignment of these protons in adduct (10).

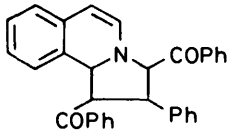
In the spectrum of the corresponding amide adduct (11a) (Thesing's intermediate) 2-H, 3-H, 5-H, 7-H, and 8-H gave signals almost identical to those of (10), but 6-H, 8a-H, and 1-H were obscured by mutual overlap. The pentadeuteriated amide adduct (16b) showed 1-H as a 9 Hz doublet, and 2-H and 3-H as a doublet and double doublet respectively, confirming that the amide adduct had an analogous structure to the ester (10). All the other adducts (9) and (11) also gave similar δ and J values (Table 5), indicating their common regio- and stereo-chemistry. The adduct (12a) from the 2-picolinium salt (7d) gave a spectrum from which the 5-H signal was absent.

The ester, amide, and nitrile adducts (13a—h), (14a—e), and (15a—e) derived from isoquinolinium salts all gave similar ^{1}H n.m.r. spectra, in which the isolated vinyl protons 5-H and 6-H gave low field doublets at δ 6.4 and 5.6 ($J_{5,6}$ 7—8 Hz); 3-H and 10b-H appeared at δ 4.4 and 5.2 (as 9—10 Hz doublets). In this series, $J_{1,2}$ varied between 6 and 10 Hz, thus giving 1-H and 2-H as either triplets or double doublets, at δ 4.6 and 3.9. The chemical shifts and coupling constants in the pyrrolidine ring of adducts (13)—(15) are very similar to those of adducts (9)—(11), indicating a similar regio- and stereo-chemistry of addition to the isoquinolinium ylides, as to the pyridinium ones.

The mass spectra of adducts (9a) and (11a) showed

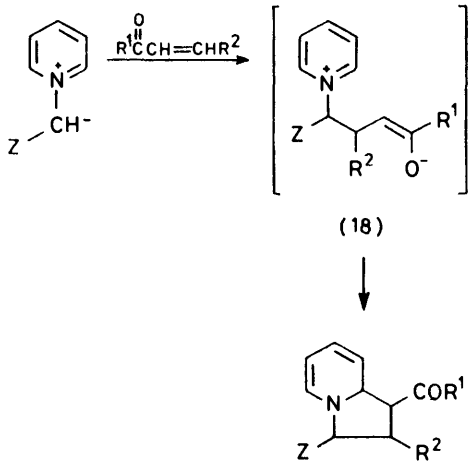
weak molecular ions (1%), with larger peaks at $M - 2$ (8%) and $M - 4$ (10%), resulting from dehydrogenations to the dihydroindolizine and indolizine. The base peaks were 77 (Ph^+) or 105 ($PhCO^+$), and ions at *m/e* 207 and 208 (chalcone) were prominent, indicating retro-cycloaddition to be the major fragmentation pathway.

Other Examples in the Literature.—The reaction of 2-phenacylisoquinolinium bromide (8d) with chalcone and sodium hydroxide is reported [9] to give an ylide analogous to (1). We have found that the spectra of this compound (Table 6) are, however, in accord with the structure (17). In this adduct 3-H resonates at 1 p.p.m. lower field than in (13)—(15): all other signals are similar. We would similarly expect the ylide reported [10] to arise from the reaction of 1-(carbamoylmethyl)-pyridinium chloride with 4-picolylideneacetophenone and sodium hydroxide to be of the structural type (11).



(17)

Mechanism of Formation of Tetrahydroindolizines.—The adducts (9)—(17) could possibly be formed by a concerted cycloaddition,[3] but it is more probable that the carbonyl-stabilised cyclic azonium methylide undergoes a Michael addition onto the chalcone, giving a reactive enolate (18), which rapidly ring-closes onto the heterocyclic ring to give the bicyclic adduct (Scheme 2). This is in agreement with the observed regiospecificity of addition, and the acid–base mediated interconversion with the open-chain salt which has been reported [8] for similar tetrahydroindolizines.



(18)

SCHEME 2

EXPERIMENTAL

M.p.s were determined with a Reichert apparatus. Spectra were recorded with a Perkin-Elmer 297 grating spectrophotometer, a Kratos MS 25 mass spectrometer, and a Varian HA-100 (100 MHz) n.m.r. spectrometer. The 220 MHz n.m.r. spectrum was obtained from the PCMU, Harwell.

General Procedures for Preparation of Cyclic Azonium Salts.—(a) The heterocycle (0.2 mol), α-bromocarbonyl compound (0.2 mol), and EtOAc (25 ml) were stirred together and left overnight, and the *salt* was filtered off as a white powder which was crystallised from ethanol.

(b) The heterocycle (0.2 mol), methyl chloroacetate (0.2 mol), and EtOAc (50 ml) were heated at 80 °C for 20 h. The salt was filtered off as a white powder, and crystallised from EtOH.

(c) The heterocycle (0.2 mol), chloroacetamide (0.2 mol), and MeCN (20 g) were heated together at 80 °C for 48 h. The salt was filtered off as a white powder, which was crystallised from EtOH.

(d) The heterocycle (0.2 mol), chloroacetonitrile (0.2 mol), and Me_2CO (50 ml) were heated under reflux for 4 h. The *salt* was filtered off as a white powder, which was crystallised from EtOH.

General Procedures for Preparation of Tetrahydroindolizines.—(a) The cyclic *N*-(alkoxycarbonylmethyl)azonium salt (10 mmol), and the αβ-unsaturated ketone (10 mmol) were dissolved together in the alcohol corresponding to the ester function in the salt (30 ml), at 25—60 °C and a solution of sodium (10 mmol) in the same alcohol (5 ml) added. The solution became orange and the product crystallised rapidly, especially after seeding. After 30 min, water (10 ml) was added to remove inorganic salts, and the *adduct* filtered off to give yellow microcrystals which were washed with water (10 ml).

(b) the *N*-(aminoformylmethyl)azonium salt (10 mmol) and the αβ-unsaturated ketone (10 mmol) were dissolved in MeOH (30 ml) at 25 °C and 1M aqueous NaOH (10 ml) was added. Further water was added and the precipitate scratched as required to produce the crystalline *adduct* as a yellow powder. The adducts were crystallised from EtOH.

(c) To a stirred suspension of 1-(cyanomethyl)isoquinolinium chloride (2.5 mmol) and the αβ-unsaturated ketone (2.5 mmol) in EtOH (15 ml) at 25 °C was added dropwise 1M aqueous NaOH (2.5 mmol), and the resulting solution stirred for 2 h. Water (4 ml) was added and the *adduct* filtered off a yellow powder, which was purified by chromatography on alumina (Me_2CO).

1,3-Dibenzoyl-1,2,3,10b-tetrahydro-2-phenylbenzo[g]-*indolizine* (17).—2-Phenacylisoquinolinium bromide was condensed with chalcone as described [9] to give the adduct as small yellow needles, m.p. 154—156 °C (lit.,[9] 154—156 °C).

[0/1089 *Received*, 10*th July*, 1980]

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