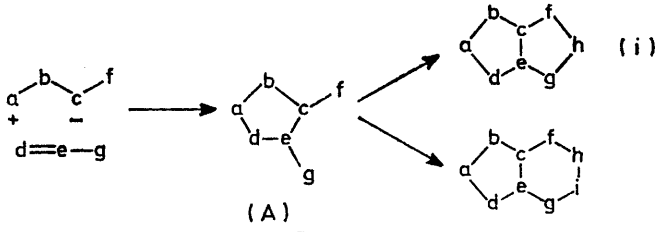
Application of Functionalised 1,3-Dipoles to the Synthesis of Fused Heterocycles

By B. Erik Landberg and J. William Lown,* Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada

A general synthetic approach to the formation of fused heterocycles, involving cycloadditions with functionalised 1,3-dipoles and subsequent ring closure, is extended to the systems 6–6, 6–6–5, 6–6–5–5, 6–6–6–5, 6–6–5–6, and 6–5–6. The regiochemistry and stereochemistry of the additions are established by specific deuterium labelling, n.m.r. spectroscopy, and chemical methods. A novel ring transformation of a 2,3-dihydrofuran to a pyridazino[4,5-*c*]pyridazine is described.

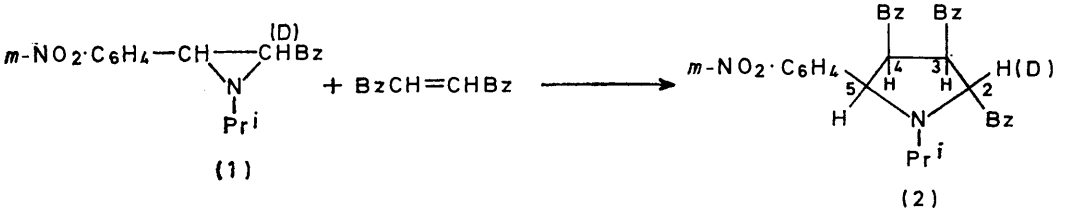
In previous papers [1-3] we described a new synthetic approach to the formation of fused heterocyclic systems employing cycloadditions with 1,3-dipoles bearing additional functionality (*i.e.* in addition to their basic 4 π-electron reactive system) to form two-ring fused heterocycles (see Scheme). This approach proved useful in the



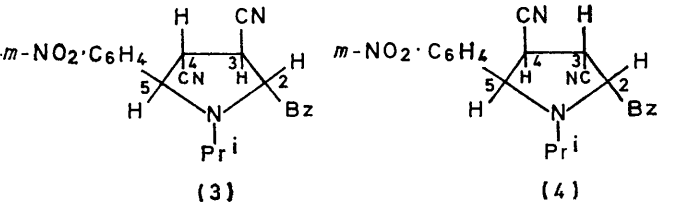
SCHEME

formation of 5–5, 5–6, 5–5–5, and 6–5–6 fused heterocycles. We report an extension of this general synthetic principle to the formation of 6–6–5, 6–6–5–5, 6–6–6–5, and 6–6–5–6 systems as well as novel examples of 5–6 and 6–5–6 systems together with a new ring transformation. Successful application of the Scheme requires (i) appropriate regiochemistry and (ii) suitable stereochemistry in the formation of intermediate (A). In order to examine these aspects further, some cycloadditions were carried out initially with azomethine ylides generated by electrocyclic cleavage of aziridines.[4,5]

2-Benzoyl-1-isopropyl-3-(3-nitrophenyl)aziridine (1) [6] reacted with (*Z*)-dibenzoylethylene in refluxing benzene to afford a single product, the *trans,cis,cis*-pyrrolidine (2). The methine n.m.r. coupling constants obtained by spin decoupling were $J_{2,3}$ 2, $J_{3,4}$ 7, and $J_{4,5}$ 10 Hz. Specific deuterium labelling [6] of the 2-proton in (1) permitted an unequivocal assignment of the methine H-2 signal in (2). Initially the H-4 and -5 signals were superimposed at δ 5·44, but they were clearly resolved after treatment with the shift reagent Eu(fod)$_3$, allowing determination of the individual coupling constants. Treatment of compound (2) with base resulted in epimerisation at position 4 to afford the all-*trans*-isomer previously obtained by cycloaddition of (1) with (*E*)-dibenzoylethylene.[1] In the latter reaction the two possible stereoisomeric products (*trans,trans,trans*- and *cis,trans,cis*) were formed in the ratio 78 : 22. The analogous reaction of the aziridine (1) with fumaronitrile afforded a mixture of the stereoisomeric pyrrolidines (3) and (4) in the ratio 95 : 5. Stereochemistry of the type shown in (4) was that required for subsequent development of the second, fused ring in the 2,3-position, with, for example, hydrazine. It is apparent that the stereochemistry of the cycloadditions is controlled by a combination of steric and electronic factors.



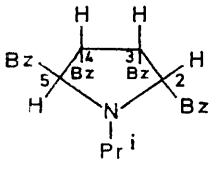
The reaction between 2,3-dibenzoyl-1-isopropylaziridine and (*Z*)-dibenzoylethylene afforded a single stereoisomer (5) which was assigned the *cis,cis,trans*-stereochemistry on the basis of the observed coupling constants: $J_{2,3}$ 1, $J_{3,4}$ 4, and $J_{4,5}$ 0. The alternative



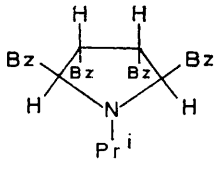
structure (6) may be ruled out by symmetry considerations and is also unlikely for mechanistic reasons since

[1] J. W. Lown and B. E. Landberg, *Canad. J. Chem.*, 1974, **52**, 798.
[2] J. W. Lown and M. H. Akhtar, *Canad. J. Chem.*, 1972, **50**, 2236.
[3] J. W. Lown and M. H. Akhtar, *J.C.S. Perkin I*, 1972, 1459.
[4] R. Huisgen, W. Scheer, G. Szeimies, and H. Huber, *Tetrahedron Letters*, 1966, 397.
[5] R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, 1967, **89**, 1753.
[6] G. Dallas, J. W. Lown, and J. P. Moser, *J. Chem. Soc.* (*C*), 1970, 2383.

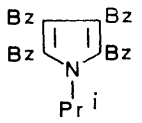
cis-azomethine ylides are trapped only rarely and only by very reactive dipolarophiles.[7] Compound (5) was



(5)



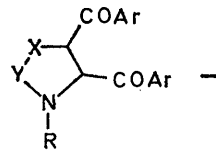
(6)



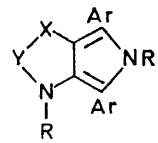
(7)

sensitive to oxidation: attempted Paal–Knorr condensation[8] with either isopropylamine or cyclohexylamine gave the pyrrole (7), which could also be obtained by reaction of (5) with tetrachloro-1,4-benzoquinone.

provides a new route to an imidazo[4,5-*d*]pyridazine (12). The regiochemistry and stereochemistry of the addition to form the imidazoline (10) were proven chemically. The lack of reaction of (10) with hydrazine



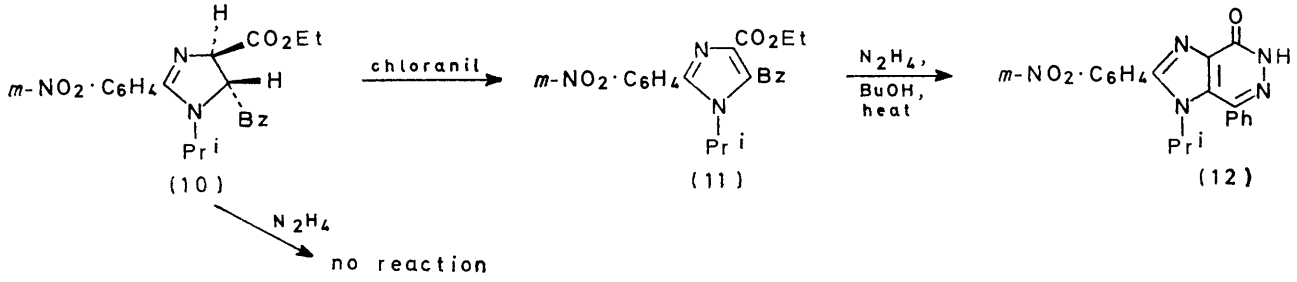
(8)



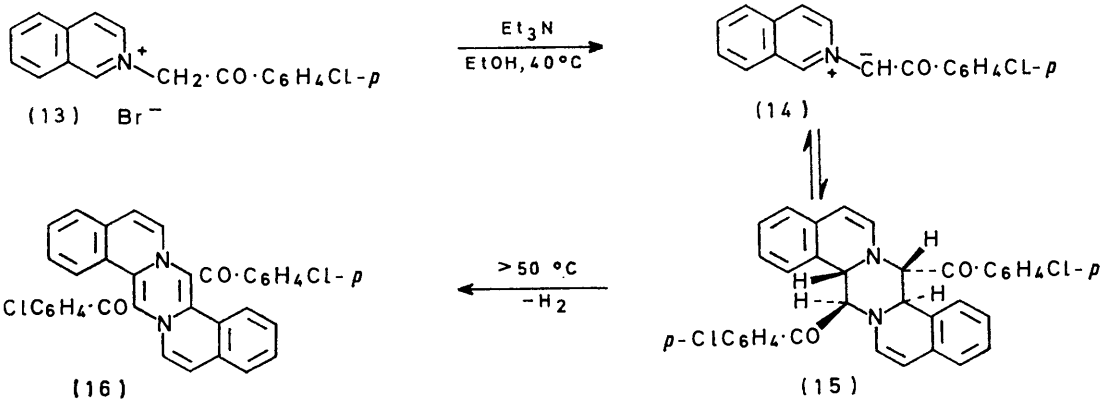
(9)

contrasted with the reactivity of the imidazole (11) indicates a *trans*-disposition of the 4- and 5-substituents. Dehydrogenation of (10) with chloranil gives (11), and ring closure of the latter with hydrazine affords the imidazopyridazine (12) and at the same time confirms the regiochemistry of the initial cycloaddition.

Application of isoquinolinium[9] and analogous pyridinium ylides[9] to the general Scheme has the added



(10) (11) (12)



(13) (14) (15) (16)

We have also observed that the reactivity of various aroyl-substituted five-membered heterocycles with amines to form the additional fused ring(s) in the Paal–Knorr condensation is sensitive to the nature of the atoms in the ring. Paal–Knorr condensation occurs if X–Y in structure (8) is O–C, C=N, or C–O, but not C–C unless this is activated by four aroyl substituents on the pyrrolidine ring.

Reaction of the aziridine (1) with ethyl cyanoformate

advantage of permitting ring closure to the reactive 3,4-double bond of the isoquinoline and extending the scope of the synthesis. Treatment of the *p*-chlorophenacylisoquinolinium bromide (13) with triethylamine afforded an orange solid which proved to be the dimer (15) of the azomethine ylide (14). The n.m.r. spectrum of compound (15) showed methine absorption as an AB quartet centred at δ 5·54 and 5·63 (*J* 8 Hz) due to the

[7] R. Huisgen, W. Scheer, H. Mader, and E. Brunn, *Angew. Chem. Internat. Edn.*, 1969, **8**, 604.

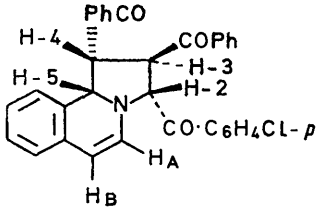
[8] (*a*) C. Paal, *Ber.*, 1884, **17**, 2756; (*b*) L. Knorr, *ibid.*, p. 2863.

[9] Y. Kobayashi, T. Kutsuma, and Y. Sekine, *Tetrahedron Letters*, 1972, 3325.

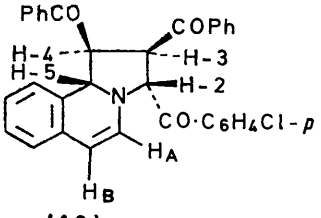
3- and 4-isoquinolinium protons and an AB quartet centred at δ 5·23 (J 11 Hz) attributed to the methines of the central tetrahydropyrazine ring. Care was necessary in isolating the dimer (15) since above 50 °C it tends to undergo dehydrogenation readily to give the pyrazino-[2,1-*a*:5,4-*a'*]di-isoquinoline (16) as a stable yellow solid, m.p. 225°.

Dimerisation of 1,3-dipoles is observed rarely and is usually a reversible process.[10] The ready dehydrogenation of (15) [to (16)] renders this compound unsatisfactory as a source of the 1,3-dipole so that generation *in situ* from (13) was preferred.

Reaction of the salt (13) with (*E*)-dibenzoylethylene in the presence of triethylamine gave the *trans,trans*-dibenzoyl-(4-chlorobenzoyl)-tetrahydropyrrolo[2,1-*a*]-isoquinoline (17) in 80% yield. The methine n.m.r.

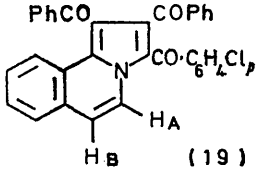


(17)
ttc

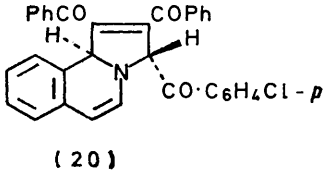


(18)
tct

assignments and the stereochemistry were established by specific deuterium labelling [H^{-3} of (17)] and double irradiation (see Table 3) which allowed determination of the individual methine coupling constants as $J_{2.3}$ 3, $J_{3.4}$ 7, $J_{4.5}$ 9 Hz, consistent with a *trans*-2,3,*trans*-3,4,*cis*-4,5-configuration.* The analogous product (18) obtained by cycloaddition of (14) to (*Z*)-dibenzoylethylene exhibited methine coupling constants ($J_{2.3}$ 3, $J_{3.4}$ 11, $J_{4.5}$ 5 Hz) consistent with a *trans*-2,3,*cis*-3,4,*trans*-4,5-configuration. It appears probable that the initial products corresponding to trapping of the *trans*-azomethine ylide suffer epimerisation at position 2 in each case to give (17) and (18), in which H-2 and -5 are *cis*-disposed.[11] Compounds (17) and (18) were dehydrogenated with tetrachloro-1,4-benzoquinone to the same pyrrolo[2,1-*a*]isoquinoline (19), which was synthesised



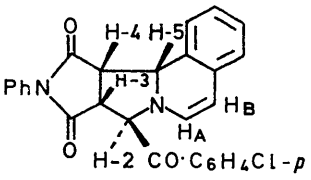
(19)



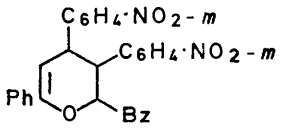
(20)

independently by reaction of (14) with dibenzoylacetylene under nitrogen [a mixture of (19) and (17) is produced by disproportionation of the initially formed pyrroline (20)].

Compound (18) slowly undergoes epimerisation at position 4 (pyrrolidine numbering) to give the *trans,trans,cis*-isomer (17) when kept in dimethyl sulphoxide for several hours, or more rapidly in the presence of triethylamine. In the case of the tetrahydropyrrolo-[3',4':3,4]pyrrolo[2,1-*a*]isoquinolinedione (21) formed by the reaction of (14) with *N*-phenylmaleimide, the methine coupling constants ($J_{2.3}$ 0, $J_{3.4}$ 8, $J_{4.5}$ 8 Hz) are consistent with a *trans,cis,cis*-configuration. Here



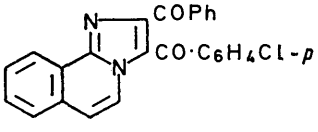
(21)



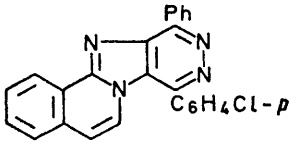
(22)

evidently the *trans*-disposition of H-2 and -5 represents the more stable configuration. Although the isoquinolinium ylide (14) reacts readily with highly activated dipolarophiles it is not sufficiently reactive to trap chalcones, which instead dimerise to form dihydropyrans such as (22) by Diels–Alder addition.[12]

Similar reaction of the ylide (14) with benzoyl cyanide afforded the imidazo[2,1-*a*]isoquinoline (23). In this instance, as in the preparation of compounds (19) and (33), spontaneous dehydrogenation took place to afford the fully aromatised (23) *via* the intermediate imidazoline. Ready ring closure of (23) with hydrazine in ethanol to form the pyridazinoimidazoisoquinoline (24) showed that

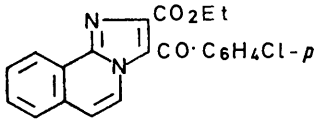


(23)

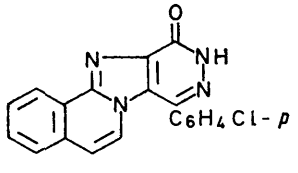


(24)

cycloaddition had taken place with the desired regiochemistry. Reaction of the ylide (14) with ethyl cyanoformate gave the imidazoisoquinoline (25), the

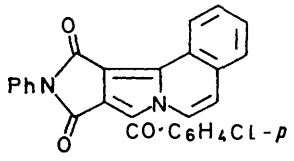


(25)



(26)

regiochemistry of which was proven by ring closure with hydrazine to give the fixed pyridazinone (26).

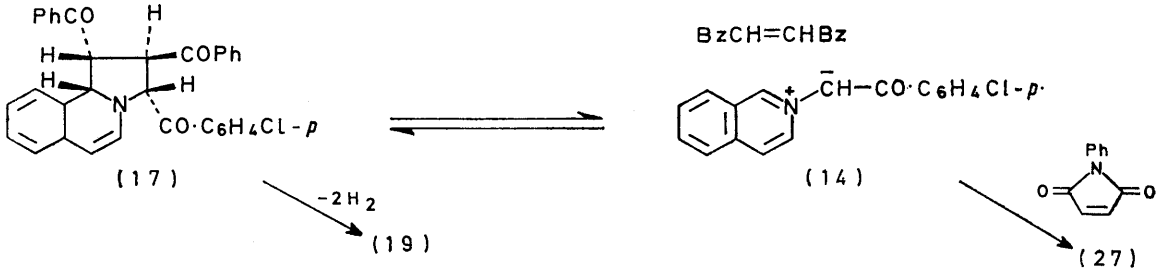


(27)

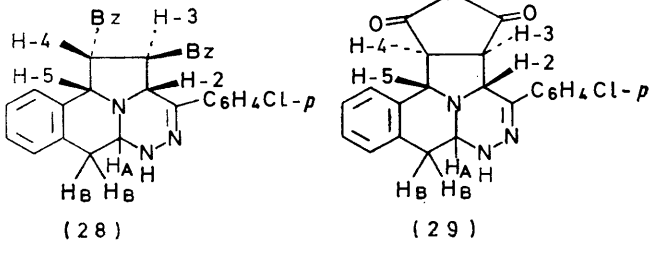
* For covenience in the presentation and comparison of n.m.r. data, the numbering of the methane protons in (17) and other heterocycles conforms with that of the parent pyrrolidine (2).

[10] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 582.
[11] P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, 1970, **35**, 888.
[12] J. Colonge and G. Descotes in ' 1,4-Cycloaddition Reactions —The Diels–Alder Reaction in Heterocyclic Synthesis,' ed. J. Hamer, Academic Press, New York, 1967, p. 217.

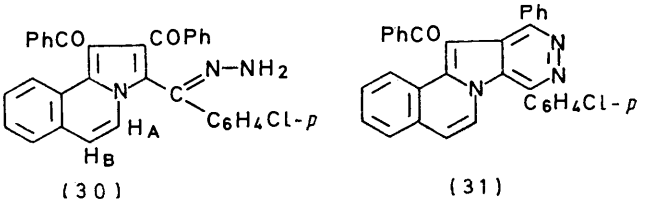
Compound (21), as in the cases of (17) and (18), was readily dehydrogenated with chloranil to compound (27). During this study it was observed that (17) turned dark red at its m.p. To determine whether this indicated dehydrogenation or cycloreversion,[13] (17) was heated in refluxing mesitylene with an excess of *N*-phenylmaleimide, a more reactive dipolarophile than (*E*)-dibenzoylethylene.[10] Compound (27) was produced in 70% yield, corresponding to exchange of dipole and loss of hydrogen at the elevated temperature. Such exchanges of dipolarophiles have been reported but are rare.[13] In addition *ca.* 20% of dehydrogenation product (19) was formed. The *N*-phenylmaleimide can act as a hydrogen acceptor at higher temperatures in these dehydrogenations.[14]



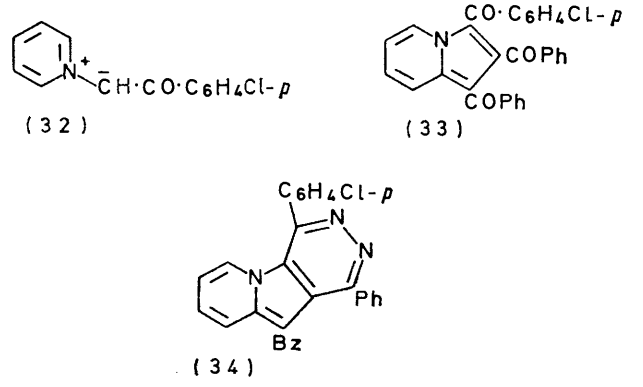
By analogy with compounds (11), (23), and (25) it was considered that the pyrroloisoquinoline (18) should react with hydrazine across the two *cis*-oriented benzoyl groups. However both isomers (17) and (18) react with hydrazine in refluxing ethanol to afford the same compound (28). The n.m.r. spectrum reveals four pyrrolidine methine proton signals still present as an AB quartet ($J_{2.3}$ 4, $J_{3.4}$ 0·5, $J_{4.5}$ 6 Hz), corresponding to a *trans,trans,cis*-configuration, and three additional methine proton signals [triplets H_A δ 5·27 and H_B (2) δ 3·08]. The i.r. spectrum exhibits an NH absorption at 3400 cm^{-1}. The mass spectrum shows loss of PhCO (105) but not of *p*-ClC_6H_4·CO (139). These data and a literature precedent [15] indicate structure (28) for this product. Compound (29) was similarly prepared from (27).



The reaction of compounds (19) and (23) with hydrazine took a different course. Compound (19) with hydrazine gave the hydrazone (30). This structure is preferred because of the absence of an *m/e* 139 peak which would be expected for *p*-ClC_6H_4·CO. The latter compound upon heating in xylene afforded the pyridazine (31). Compound (23) afforded (24) directly on treatment with hydrazine. In these latter cases the driving force provided by formation of a completely aromatised system dictates the direction of cyclisation.



The analogous pyridinium ylides behave differently from the isoquinolinium ylides and provide a novel alternative approach to two-ring fused heterocycles. Compound (32) reacted with dibenzoylacetylene with concomitant dehydrogenation of the intermediate to give the indolizine (33). Reaction of (33) with hydrazine afforded the pyridazino[4,5-*b*]indolizine (34). The direction of cyclisation is confirmed unambiguously by the mass spectrum which shows *m/e* 111 (C_6H_4Cl) and 105 (COPh). The analogous reactions with (*E*)- or (*Z*)-dibenzoylethylene afforded the 2,3-dihydrofurans (35) by initial Michael addition followed by internal displacement of pyridine by the enolate. Literature precedents for this process involve the reaction of



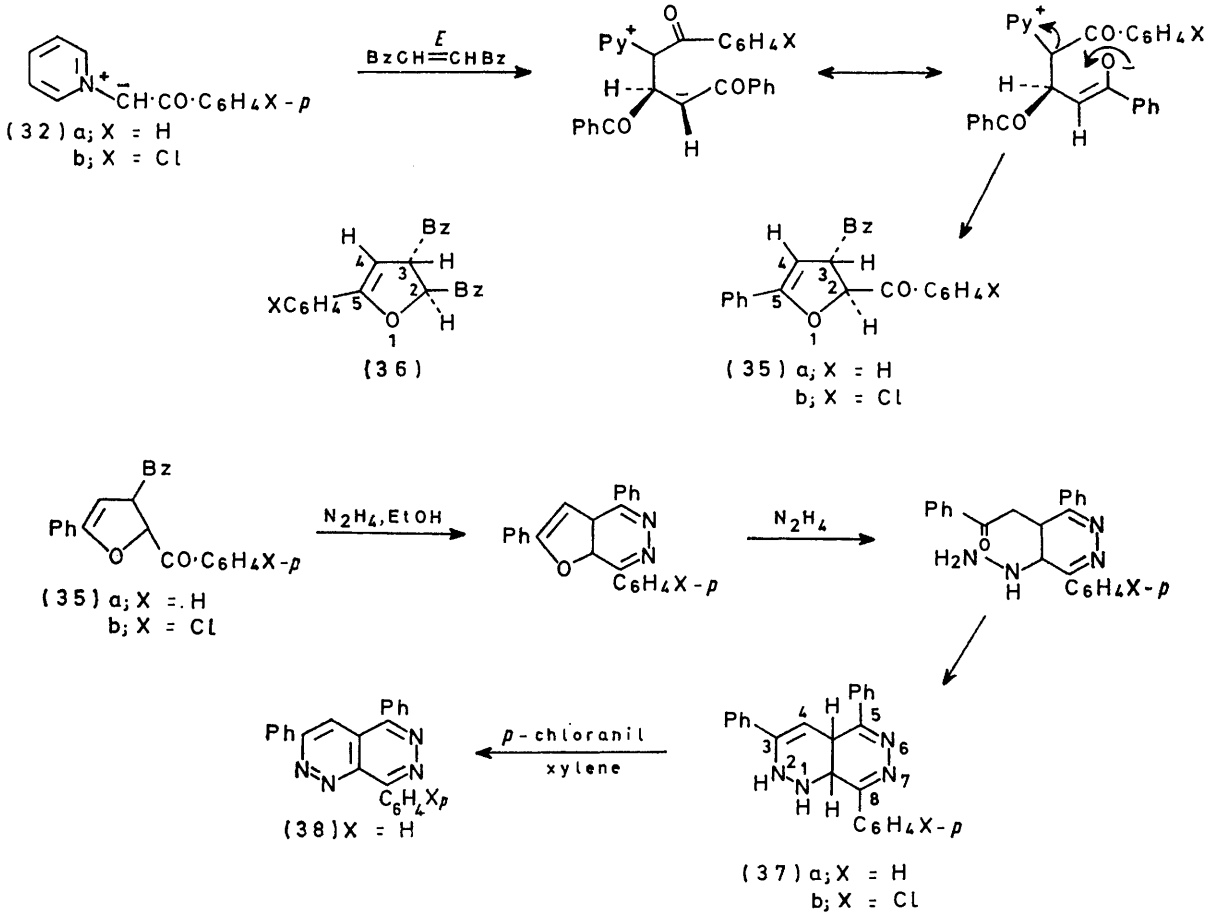
[13] J. W. Lown, R. K. Smalley, G. Dallas, and T. W. Maloney, *Canad. J. Chem.*, 1970, **48**, 103.

[14] L. M. Jackman, *Adv. Org. Chem.*, 1960, **2**, 348.

[15] F. Krohnke, *Angew. Chem. Internat. Edn.*, 1963, **2**, 236.

sulphonium ylides with acetylenic esters to produce furans.[16]

In the n.m.r. spectrum of the dihydrofuran (35a) two methine singlets appeared at δ 6·60 and 8·57. Assignment of the latter to H-2 was confirmed by deuterium labelling of the ylides (32), and the zero coupling signifies a *trans*-configuration. Additional evidence favouring (35) over the alternative structure (36) is a strong mass spectral peak at *m/e* 139 (*p*-ClC_6H_4·CO). Reaction of the dihydrofurans (35a and b) with hydrazine in refluxing ethanol resulted in a novel ring transformation[17] to



afford products (37a and b) which contained no oxygen. Evidence for the tetrahydropyridazino[4,5-*c*]pyridazine structure (37a) includes NH n.m.r. peaks at δ 5·45 (as well as a 3300 cm^{-1} i.r. absorption) and a signal for two bridgehead methine protons at δ 4·02. Dehydrogenation of (37a) with *p*-chloranil afforded the pyridazino-[4,5-*c*]pyridazine (38).

EXPERIMENTAL

M.p.s were determined with a Fisher–Johns apparatus. I.r. spectra were recorded with a Perkin-Elmer 421 spectrophotometer. N.m.r. spectra were measured on Varian A-60 and A-100 spectrometers for *ca.* 10—15% (w/v) solutions, usually in $CDCl_3$, with tetramethylsilane as a standard. Mass spectra were determined with an A.E.I. MS-9 double-focusing high resolution spectrometer (ionisation energy usually 70 eV). Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15,000. Kieselgel DF-5 (Camag) and Eastman Kodak precoated sheets were used for t.l.c. Microanalyses were carried out by Mrs. D. Mahlow of this department.

General Preparation of 2-Aroyl- and 2,3-Diaroyl-aziridines.—These compounds were prepared by established methods involving Claisen–Schmidt condensations to form chalcones, followed by bromination to afford dibromochalcones and finally treatment with primary amines to give the aroylaziridines.[18]

(Z)-1,2-*Dibenzoylethylene*—This compound, m.p. 128—130°, was prepared quantitatively from commercially available (*E*)-dibenzoylethylene (4 g) by irradiation of a solution in acetone (150 ml) for 12 h with a medium-pressure mercury lamp (lit.,[19] m.p. 133—134°).

Dibenzoylacetylene.—A solution of 1,2-dibenzoyl-1,2-dibromoethane (59 g, 0·15 mol) and purified triethylamine (36 g, 0·34 mol) in acetone (20 ml) was heated under reflux for 1 h, then cooled. The precipitated triethylammonium

[16] (*a*) M. Takaku, Y. Hayashi, and H. Nozaki, *Tetrahedron Letters*, 1969, 2053; (*b*) E. Winterfeldt, *Ber.*, 1965, **98**, 1581.

[17] *Cf.* H. C. Van der Plas, ' Ring Transformations in Heterocycles,' vol. 1, Academic Press, New York, 1973, p. 194.

[18] J. W. Lown, G. Dallas, and T. Maloney, *Canad. J. Chem.*, 1969, **47**, 3557.

[19] L. Horner and E. Lingnau, *Annalen*, 1955, **591**, 21.

bromide was collected and the filtrate was concentrated *in vacuo* to afford the crude dibenzoylacetylene (from 98% ethanol) (25 g, 72%), m.p. 110—111° (lit.,[20] 110—111°).

2-(4-*Chlorophenacyl*)*isoquinolinium Bromide* (13).—This compound, together with other isoquinolinium and pyridinium salts, was prepared [21] from equivalent quantities of heterocyclic base and phenacyl bromide in a stirred dilute solution in tetrahydrofuran (24 h). Careful treatment of 2-(4-chlorophenacyl)isoquinolinium bromide (13) (22 g, 40 mmol) with N-sodium hydroxide (70 ml) in ethanol (60 ml) at 45—50 °C for 3 min gave 8,16-*bis*-(p-*chlorobenzoyl*)-8,8a,-16,16a-*tetrahydropyrazino*[2,1-a:5,4-a′]*di-isoquinoline* (15) (15 g, 45%) as an orange solid, m.p. 175° [Found: C, 71·65; H, 4·5; Cl, 13·25; N, 5·05%; $(M - C_9H_7N - H_2O)^+$, 415·0518. $C_{34}H_{24}Cl_2N_2O$ requires C, 71·5; H, 4·3; Cl, 12·65; N, 5·0%. $C_{25}H_{15}Cl_2N$ requires *m/e* 415·0532]; $\nu_{max.}$ (Nujol) 1667 cm^{-1} (C=O).

This compound was readily dehydrogenated if the temperature rose above 50 °C during isolation to afford 8,16-*bis*-(4-*chlorobenzoyl*)*pyrazino*[2,1-*a*:5,4-a′]*di-isoquinoline* (16) as a yellow solid, m.p. 223—225° (Found: M^+, 558·0895. $C_{34}H_{20}Cl_2N_2O_2$ requires M, 558·0901); $\nu_{max.}$ ($CHCl_3$) 1600 cm^{-1} (C=O); $\lambda_{max.}$ 269 nm (ε 1500).

4′-*chloro*-1,1,1-*trideuterioacetophenone*.—Freshly distilled *p*-chloroacetophenone (100 g) was stirred in a mixture of dry tetrahydrofuran (200 ml) and deuterium oxide (50 ml) with potassium hydroxide (150 mg) for 15 h. The solvent was removed and the residual oil distilled at 10 mmHg. A second pass with fresh deuterium oxide gave the product (80 g) with 80% deuterium incorporation as determined by n.m.r.

Reaction of 2-*Benzoyl*-1-*isopropyl*-3-(3-*nitrophenyl*)*aziridine* (1) *with Fumaronitrile*.—A solution of the aziridine (1·55 g, 5 mmol) and fumaronitrile (0·39 g, 5 mmol) in dry benzene (50 ml) was heated under reflux for 20 h. Concentration of the cooled solution *in vacuo* and chromatography of the residual oil on B.D.H. grade II alumina (50 g) with benzene as eluant gave 2-*benzoyl*-3,4-*dicyano*-1-*isopropyl*-5-(3-*nitrophenyl*)*pyrrolidine*. Recrystallisation from benzene–hexane (1 : 1) afforded the pure all-*trans*-isomer (3) (1·50 g, 70%), m.p. 154—155° (Found: C, 67·9; H, 5·05; N, 13·9%; M^+, 388·1538. $C_{22}H_{20}N_4O_3$ requires C, 68·0; H, 5·15; N, 13·9%; M, 388·1535); $\nu_{max.}$ ($CHCl_3$) 1675 cm^{-1} (C=O); δ($CDCl_3$) 0·9 (6H, dd, J 6 Hz, Me_2CH), 3·05 (1H, m, Me_2CH), 3·35 (1H, dd, $J_{3,4}$ 4·0, $J_{4,5}$ 6·0 Hz, H-4), 3·35 (1H, dd, $J_{3,4}$ 4·0, $J_{2,3}$ 2·0 Hz, H-3), 5·20 (1H, d, $J_{4,5}$ 6·0 Hz, H-5), 5·46 (1H, d, $J_{2,3}$ 2·0 Hz, H-2), and 7·3—8·4 (9H, m, ArH). The n.m.r. spectrum of the mother liquor revealed *ca.* 5% of the *cis,trans,cis*-isomer (4); δ($CDCl_3$) 3·81 (1H, dd, $J_{3,4}$ 7·0, $J_{2,3}$ 7·0 Hz, H-3), 4·38 (1H, dd, $J_{3,4}$ 7·0 Hz, H-3), 5·11 (1H, d, $J_{4,5}$ 11·0 Hz, H-5), and 5·60 (1H, d, $J_{2,3}$ 7·0 Hz, H-2).

2,3,4-*Tribenzoyl*-1-*isopropyl*-5-(3-*nitrophenyl*)*pyrrolidine* (2) and 2,3,4,5-*tetrabenzoyl*-1-*isopropylpyrrolidine* (5) were prepared similarly. Spectral data including double irradiation experiments and analyses are given for these and similar compounds in the Tables.

Reaction of 2-*Benzoyl*-1-*isopropyl*-3-(3-*nitrophenyl*)*aziridine* (1) *with Ethyl Cyanoformate*.—A solution of ethyl cyanoformate (0·5 g, 5 mmol) and the aziridine (1·55 g, 5 mmol) in benzene (50 ml) was heated under reflux for 3 h, then evaporated under reduced pressure, and the residual oil was chromatographed on B.D.H. alumina (60 g). The first fraction was unchanged aziridine and the second afforded *methyl* 5-*benzoyl*-1-*isopropyl*-2-(3-*nitrophenyl*)-Δ²-*imidazoline*-4-*carboxylate* (10) (0·5 g, 26%), m.p. 116—118° (from ethanol) (Found: M^+, 409·1645. $C_{22}H_{23}N_3O_5$ requires M, 409·1638); $\nu_{max.}$ ($CHCl_3$) 1645, 1675 (C=O), 1600 (C=N), 1350, and 1530

TABLE 1

Fused heterocycles

No.	M.p. (°C) *	Yield (%)	Molecular formula	Found C (%)	Found H (%)	Found N (%)	Found Cl (%)	Found M^+	Required C (%)	Required H (%)	Required Cl (%)	Required N (%)	Required M
(2)	154—155	70	$C_{34}H_{30}N_2O_5$	74·55	5·45		4·45	546·2153	74·7	5·55		5·15	546·2156
(3)	140—142	70	$C_{32}H_{20}N_4O_3$	67·9	5·05		13·9	388·1538	68·0	5·15		13·9	388·1535
(5)	186—188	40	$C_{35}H_{31}NO_4$	79·35	5·7		2·65	529·2248	79·35	5·9		2·65	529·2253
(11)	167—168	67	$C_{22}H_{21}N_3O_5$	64·4	5·05		10·2	407·1487	64·5	5·15		10·3	407·1482
(12)	278—279	70	$C_{20}H_{17}N_5O_3$	66·55	5·1		19·35	375·1338	64·0	4·55		18·65	375·1330
(17)	189—190	80	$C_{33}H_{24}ClNO_3$	76·2	4·75	6·56	2·85	517·1433	76·45	4·65	6·85	2·65	517·1445
(18)	172—174	50	$C_{33}H_{24}ClNO_3$	76·3	4·75	6·6	2·4	517·1432	76·45	4·65	6·85	2·65	517·1445
(19)	193—194	33	$C_{33}H_{20}ClNO_3$	77·25	4·5	6·95	2·35	513·1099	77·10	3·9	6·9	2·75	513·1132
(21)	195—197 [a]	66 †	$C_{27}H_{19}ClN_2O_3$					454·1066					454·1085
(23)	115—116	15	$C_{25}H_{15}ClN_2O_2$	72·95	4·0	10·15	6·65	410·0817	73·2	3·7	8·65	6·85	410·0823
(24)	287—288	60	$C_{25}H_{15}ClN_4$	73·7	4·0	10·1	13·25	406·0992	73·8	3·7	8·75	13·75	406·0986
(25)	173—174 [b]	48	$C_{21}H_{15}ClN_2O_3$	67·0	4·0	9·85	7·25	378·0772	66·6	4·0	9·4	7·4	378·0760
(26)	318—319	70	$C_{19}H_{11}ClN_4O$	65·3	3·75	10·15	15·0	346·0612	65·7	3·2	10·25	16·2	346·0622
(27)	>300	70	$C_{27}H_{15}ClN_2O_3$	70·1	4·0		5·6	450·0790	71·45	3·35	7·9	6·6	450·0772
(28)	231	33	$C_{33}H_{26}ClN_3O_2$	74·4	4·9	5·2	7·3	531·1721	74·3	4·9	6·7	7·85	531·1714
(29)	275—276	60	$C_{27}H_{21}ClN_4O_2$	69·5	4·45	8·2	11·45	468·1362	69·15	4·5	7·6	11·95	468·1354
(30)	276—278	60 ‡	$C_{33}H_{22}ClN_3O_2$	73·7	4·55		7·15	527·1420	74·6	4·2		7·95	527·1401
(31)	278—280	100	$C_{33}H_{20}ClN_3O$	76·85	4·0	9·25	7·1	509·1282	77·75	3·95	6·95	8·25	509·1296
(33)	197—199	65	$C_{29}H_{18}ClNO_3$					463·0967					463·0976
(34)	251—255 [c]	30	$C_{29}H_{16}ClN_3O$	76·0	4·15		9·05	459·1123	75·9	3·95		9·15	459·1139
(35a)	116—119	70	$C_{24}H_{18}O_3$	80·35	5·25			354·1250	81·1	5·1			354·1255
(35b)	143—144	55	$C_{24}H_{17}ClO_3$	74·55	4·5	10·3		388·0861	74·25	4·4	9·15		308·0865
(37a)	171—173	60 §	$C_{24}H_{20}N_4$	78·45	5·55		15·0	364·1697	79·05	5·5		15·35	364·1688
(37b)	196—200	50 §	$C_{24}H_{19}ClN_4$	69·55	5·1	10·3	13·15	398·1295	69·2	5·05	8·55	13·45	398·1298
(38)	(Oil)	35	$C_{24}H_{16}N_4$					360·1370					360·1375
(10)	116—118 [c]	50	$C_{22}H_{23}N_3O_5$					409·1645					409·1638

* From benzene–hexane unless stated otherwise: [a] from chloroform; [b] from ethanol–benzene; [c] from ethanol. † Contaminated with Et_3NHBr. ‡ Contaminated with some cyclised product (31). § Monohydrate.

[20] R. E. Lutz and W. R. Smithey, *J. Org. Chem.*, 1951, **16**, 51.
[21] F. Krohnke, *Ber.*, 1935, **68**, 1117.

cm^{-1} (NO_2); δ($CDCl_3$) 1·2 (6H, t, *Me*$_2$CH), 1·4 (3H, t, *Me*CH$_2$), 3·50 (1H, m, Me$_2$C*H*), 4·40 (2H, q, C*H*$_2$Me), and 7—8·8 (11H, m, ArH and methines). That the product was a Δ^2- and not a Δ^3-imidazoline was indicated by the position of the isopropyl methine signal.[1]

$C_{20}H_{17}N_5O_3$ requires C, 66·0; H, 4·55; N, 18·65%; *M*, 375·1330); $\nu_{max.}$ (Nujol) 1660 (C=O), 3360 (NH), 1535, and 1370 cm^{-1} (NO_2); δ[$(CD_3)_2SO$] 1·01 (6H, d, *Me*$_2$CH), 4·15 (1H, septet, Me$_2$C*H*), 5·3br (1H, s, NH), and 6·7—7·6 (9H, m, ArH).

TABLE 2

Spectroscopic data for fused heterocycles (pyrrole-type numbering where appropriate)

	δ						*J*/Hz				
No.	H-2	H-3	H-4	H-5	H_A	H_B	2,3	3,4	4,5	A,B	$\nu_{max.}$(CHCl$_3$)/cm^{-1}
(2)	5·73d	4·15q	5·42t	5·46d			2·0	7·0	10·0		1670 (C=O
(3)	5·46d	3·45q	3·35q	5·20d			2·0	4·0	6·0		1675 (C=O), 2240 (C≡N)
(4)	5·60d	3·81q	4·38q	5·11d			7·0	7·0	11·0		1675 (C=O)
(6)	(*ca.* 7·5d) *	5·10d †	5·69d †	*ca.* 7·5d			*ca.* 1	4·0	0	2 †	1670 (C=O)
(17)	5·72d	5·12q	4·90t	4·55d	5·50d	6·67d	3·0	7·0	9·0	7·0	1670 (C=O)
(18)	5·41d	5·20q	4·76t	4·76d	5·60d	6·30d	3·0	11·0	5·0	7·0	1670 (C=O)
(19)				*ca.* 7·5	9·05d					8·0	1660 (C=O)
(21)	5·82s	4·78d	3·63t	4·11d	5·40d	6·60d	0·0	8·0	8·0	7·0	1710 (C=O)
(28)	4·25d †	2·46d †	3·64d	5·27d	5·27d	3·08t	4·0	0·5	6·0	3	1670 (C=O), 3400 (NH)
(29)	5·15d	3·50q †	2·80q †	4·72d	4·90s	4·10t	5·0	7·0	5·0	<0·5	1710 (C=O), 3400 (NH)
(30)					6·85d	8·21d				8·0	1655 (C=O), 3400 (NH)
(35a)	8·57s	6·60s	(*ca.* 7—8) *						0·0		1660 (C=O)
(35b)	8·52	6·55s	(*ca.* 7—8) *						0·0		1660 (C=O)
(37a)		[4·0s (H-4a and -8a)]									3300 (NH)
(37b)		[4·04s (H-4a and -8a)]									3300 (NH)

* Indicates signals of methine or vinyl protons obscured by those of aromatic protons. † Tentative assignments.

Methyl 5-Benzoyl-1-isopropyl-2-(3-nitrophenyl)imidazole-4-carboxylate.—The imidazoline (10) (0·3 g, 0·73 mmol) was readily dehydrogenated with chloranil (0·15 g, 0·61 mmol) in refluxing xylene (50 ml) over 3 h. The residue was chromatographed on B.D.H. alumina (2% EtOH–CH_2Cl_2 as eluant) to give the *imidazole* (11) (0·2 g, 67%), m.p. 167—168° (Found: C, 64·4; H, 5·05; N, 10·22%; *M*$^+$, 407·1487. $C_{22}H_{21}N_3O_5$ requires C, 64·5; H, 5·15; N, 10·3%; *M*, 407·1482); $\nu_{max.}$ ($CHCl_3$) 1720, 1665 (C=O), 1535, and 1350 cm^{-1} (NO_2); δ($CDCl_3$) 1·0 (3H, t, Me), 1·45 (6H, d, *Me*$_2$CH), 4·10 (2H, q, *CH*$_2$Me), 4·56 (1H, m, Me$_2$C*H*), and 7·2—8·5 (9H, m, ArH).

TABLE 3

Double irradiation experiments at 100 MHz

Compound	Proton irradiated	Decoupling frequency (Hz)	Lines collapsed: Original form	Lines collapsed: Final form	Measured remaining coupling (Hz)
(2)	H-2	573	4·15q	d	$J_{3,4}$ 7·0
	H-4, -5	548	4·15q	s	$J_{2,3}$ 0·0
	H-3	415	5·73q	s	
(3)	H-2	546	3·45q	d	$J_{3,4}$ 4·0
	H-5	517	3·35q	d	$J_{3,4}$ 4·2
	H-3	349	5·46d	s	
	H-4	335	5·20d	s	
(17)	H_B	667	5·50d	s	
	H_A	550	6·67d	s	
	H-2	572	5·12q	d	$J_{3,4}$ 7·00
	H-4	490	4·55d	s	
(28)	H_A	308	5·27t	s(br)	
	H-4	375	5·27d	s	
	H-3	247	4·25d	s	
	H-5	526	3·72d	s	
	H_B	526	3·08t	d	$J_{A,B}$ 3·00

1-Isopropyl-2-(3-nitrophenyl)-7-phenyl-1H-imidazo[4,5-d]-pyridazin-4(5H)-one.—A solution of the imidazole (11) (0·2 g, 0·5 mmol) and 95% anhydrous hydrazine (2 ml) in butanol (50 ml) was heated under reflux for 14 h. The precipitate was collected, washed, and dried affording the *imidazopyridazine* (12) (0·15 g, 82%), m.p. 278—280° (Found: C, 66·55; H, 5·1; N, 19·35%; *M*$^+$, 375·1338.

2,3,4,5-Tetrabenzoyl-1-isopropylpyrrole (7).—A solution of 2,3,4,5-tetrabenzoyl-1-isopropylpyrrolidine (5) (0·268 g, 0·506 mmol) and tetrachloro-1,4-benzoquinone (0·250 g, 1·02 mmol) in toluene (50 ml) was heated under reflux for 3 h. Evaporation of the solvent and chromatography of the residual oil on B.D.H. alumina gave the *pyrrole* (7) (0·25 g, 95%), m.p. 211—213° (from ethanol–benzene) (Found: C, 79·9; H, 5·0; N, 2·8%; *M*$^+$, 525·1935. $C_{35}H_{27}NO_4$ requires C, 79·9; H, 5·15; N, 2·65%; *M*, 525·1940); $\nu_{max.}$ ($CHCl_3$) 1645 cm^{-1} (C=O); δ($CDCl_3$) 1·54 (6H, d, *Me*$_2$CH), 5·10 (1H, m, Me$_2$C*H*), and 7—7·8 (20H, m, ArH).

trans,trans-1,2-*Dibenzoyl-3-(p-chlorobenzoyl)-1,2,3,10b-tetrahydropyrrolo*[2,1-a]*isoquinoline* (17).—A solution of 2-(4-chlorophenacyl)isoquinolinium bromide (13) (3·62 g, 10 mmol) and (*E*)-1,2-dibenzoylethylene (2·36 g, 10 mmol) in warm (60 °C) pyridine (100 ml) was treated with triethylamine (5 ml) and set aside at room temperature for 8 h. The filtered solution was concentrated *in vacuo*. The residual red oil crystallised from hexane–benzene to afford the *pyrroloisoquinoline* (17) as yellow crystals (4·0 g, 80%), m.p. 186—190° (decomp.) (Found: C, 76·2; H, 4·75; Cl, 6·56; N, 2·85%; *M*$^+$, 517·1433. $C_{33}H_{24}{}^{35}ClNO_3$ requires C, 76·45; H, 4·65; Cl, 6·85; N, 2·66%; *M*, 517·1445); $\nu_{max.}$($CHCl_3$) 1670 cm^{-1} (C=O); δ($CDCl_3$) 4·55 (1H, d, $J_{1,10b}$ 9·0 Hz, H-10b), 4·90 (1H, t, $J_{1,10b}$ 9·0, $J_{1,2}$ 7 Hz, H-1), 5·12 (1H, dd, $J_{2,3}$ 3, $J_{1,2}$ 7 Hz, H-2), 5·50 (1H, d, $J_{5,6}$ 7·0 Hz, H-5), 5·72 (1H, d, *J* 3·0 Hz, H-3), 6·67 (1H, d, $J_{5,6}$ 7·0 Hz, H-6), and 7—8 (18H, m, ArH).

When the [α-^{2}H] ylide was employed the doublet at 5·72 was diminished in intensity (therefore H-3) and the quartet at 5·12 became a doublet (*J* 7·0 Hz) (therefore H-2).

Compounds (19), (21), and (25) were synthesised by similar procedures (see Table 1). The preparation of compound (17) could also be carried out with the azomethine ylide dimer (15). Compound (15) (1·12 g, 3 mmol) and (*E*)-dibenzoylethylene (0·95 g, 4 mmol) were heated at 90° in pyridine (100 ml) for 1 h. The cooled solution was concentrated *in vacuo* and the residue subjected to column chromatography on B.D.H. alumina (100 g) with benzene as

eluant. The first fraction afforded (17) (0·6 g, 29%), m.p. 186—190°.

1,2-*Dibenzoyl*-3-(4-*chlorobenzoyl*)*pyrrolo*[2,1-a]*isoquinoline* (19).—A solution of dibenzoylacetylene (1·6 g, 6·7 mmol) and 2-(4-chlorophenacyl)isoquinolinium bromide (2·48 g, 6·7 mmol) in pyridine (50 ml) and triethylamine (2 ml, 14 mmol) was heated at 60 °C for 2 h under nitrogen. The mixture was set aside at room temperature for 18 h, the precipitated methylamine hydrobromide was collected, and the concentrated filtrate was chromatographed on B.D.H. alumina with benzene as eluant. The first fraction gave (17) (0·25 g, 7·5%), m.p. 186—190°, and the second the *pyrroloisoquinoline* (19) (0·32 g, 9·5%) as a yellow solid, m.p. 190—192° (from benzene–hexane) (Found: C, 77·25; H, 4·5; Cl, 6·95; N, 2·35%; M^+, 513·1099. $C_{33}H_{20}{}^{35}ClNO_3$ requires C, 77·1; H, 3·9; Cl, 6·9; N, 2·75%; M, 513·1132); $\nu_{max.}$(CHCl$_3$) 1600 cm^{-1} (C=O); δ(CDCl$_3$) 9·05 (1H, d, J 8 Hz, H-6) and 7—8 (19H, m, ArH). The third fraction proved to be the azomethine ylide dimer (15) (0·6 g, 32%), m.p. 175°.

Attempted Reaction of the 2-(4-*Chlorophenacyl*)*isoquinolinium Ylide with a Chalcone*.—A suspension of 2-(4-chlorophenacyl)isoquinolinium bromide (2·5 g, 6·6 mmol), 3-(3-nitrophenyl)-1-phenylprop-2-en-1-one (1·85 g, 7·3 mmol), and triethylamine (5 ml, 36 mmol) in dichloromethane (150 ml) was refluxed for 18 h, then cooled. The resulting precipitate was collected and washed with water, then with hot chloroform, affording 2-*benzoyl*-2,3-*dihydro*-2,3-*bis*-(3-*nitrophenyl*)-6-*phenylpyran* (22) as a white solid (0·7 g, 40%), m.p. 275—276° (Found: C, 70·75; H, 4·33; N, 2·5%; M^+, 506·1475. $C_{30}H_{12}N_2O_6$ requires C, 71·1; H, 4·35; N, 5·5%; M, 506·1478); $\nu_{max.}$ (KBr) 1660s (C=O), 1520s, 1350s (NO_2), and 1650 cm^{-1} (C=C).

Reaction of the Tetrahydropyrroloisoquinoline (17) *with Hydrazine*.—A solution of the tetrahydropyrroloisoquinoline (1·0 g, 0·2 mmol) and 64% hydrazine solution (4 ml, 91 mmol) in ethanol (50 ml) was heated under reflux for 4 h then allowed to cool. The resulting white precipitate was collected and washed with cold ethanol to give 1,2-*dibenzoyl*-3-p-*chlorophenyl*-2,2a,5,5a,6,10b-*hexahydro*-1H-4,5,-10c-*triaza-aceanthrylene* (28) (0·3 g, 33%), m.p. 231—232° (Found: C, 74·4; H, 4·9; Cl, 5·20; N, 7·32%; M^+, 531·1721, $C_{33}H_{26}{}^{35}ClN_3O_2$ requires C, 74·3; H, 4·9; Cl, 6·7; N, 7·5%; M, 531·1714); $\nu_{max.}$ (Nujol) 1670 (C=O) and 3400 cm^{-1} (NH); δ[(CD$_3$)$_2$SO] [for numbering see formula (28)] 2·46 (1H, d, $J_{2,3}$ 4·0 Hz, H-3), 3·08 (2H, t, J 3 Hz, H_B), 3·74 (1H, d, $J_{4,5}$ 6·0, $J_{3,4}$ 0·5 Hz, H-4), 4·25 (1H, d, $J_{2,3}$ 4·0 Hz, H-2), and 5·27 (2H, m, H-5 and H_A). The signal at 5·27 can be separated into two distinct signals by addition of Eu(fod)$_3$ [2 mg with 20 mg of (28)]: δ 5·40 (1H, t, J 3·0 Hz, H_A) and 5·62 (1H, d, $J_{4,5}$ 6·0 Hz, H-5).

Reaction of compound (18) with hydrazine gave the same product (28) in comparable yield. Other reactions with hydrazine, *e.g.* to prepare compounds (12), (24), (29), (31), and (34), were carried out in similar fashion.

Dehydrogenation of the Tetrahydropyrroloisoquinoline (17) *with* p-*Chloranil*.—This reaction is typical of the dehydrogenations carried out with *p*-chloranil. A solution of the tetrahydropyrroloisoquinoline (17) (2·085 g, 4 mmol) and *p*-chloranil (2·46 g, 10 mmol) in xylene (50 ml) was heated under reflux for 3 h, cooled, and concentrated *in vacuo*. The residual oil was chromatographed on B.D.H. grade II alumina (50 g). The first fraction, an orange oil, crystallised from benzene–hexane to give the *pyrroloisoquinoline* (19) (1·4 g, 68%), m.p. 189—191°, identical with that obtained from cycloaddition of the isoquinolinium ylide to dibenzoylacetylene.

Exchange of Dipolarophiles with the Tetrahydropyrroloisoquinoline and N-*Phenylmaleimide*.—A solution of the tetrahydropyrroloisoquinoline (17) (1·035 g, 2 mmol) and *N*-phenylmaleimide (0·4 g, 2·3 mmol) in mesitylene (30 ml) was heated under reflux for 3 h. Upon cooling, a precipitate formed (0·3 g; m.p. 300°). The filtrate was chromatographed on B.D.H. alumina (50 g). The first fraction eluted with benzene (0·3 g) was identical with the precipitate first formed, which was shown by spectral comparison to be 8-p-*chlorobenzoyl*-10-*phenylpyrrolo*[3′,4′:3,4]*pyrrolo*[2,1-a]-*isoquinoline*-9,11-*dione* (27) (combined yield 67%). The second fraction (eluted with chloroform) was compound (19) (0·2 g, 20%) formed by dehydrogenation of the starting material (m.p. 193—194°).

2,3-*Dibenzoyl*-2,3-*dihydro*-5-*phenylfuran* (35a).—A solution of *N*-phenacylpyridinium bromide (7·0 g, 25mmol), (*E*)-1,2-dibenzoylethylene (6·5 g, 26 mmol), and triethylamine (9·1 g, 90 mmol) in pyridine (150 ml) was heated at 70 °C for 30 min then set aside at room temperature for several hours. The precipitated triethylamine hydrobromide was collected, the solvent was removed *in vacuo*, and the reddish brown residue was recrystallised from benzene–hexane to give the *dihydrofuran* (7 g, 70%), m.p. 116—119° (Found: C, 80·5; H, 5·25%; M^+, 354·1250. $C_{24}H_{18}O_3$ requires C, 81·1; H, 5·1%; M, 354·1244); $\nu_{max.}$ (Nujol) 1660s (C=O) and 1610s cm^{-1} (C=C); δ[(CD$_3$)$_2$SO] 6·60 (1H, s, H-3), 8·57 (1H, s, H-2), and 7—8 (16H, m, ArH). The same compound was obtained (50%; m.p. 118°) by reaction with (*Z*)-dibenzoylethylene. Deuterium incorporation (H-2) in the analogous 3-*benzoyl*-2-p-*chlorobenzoyl*-2,3-*dihydro*-5-*phenylfuran* (35b) by using 4-chloro[α-^{2}H]phenacyl pyridinium bromide resulted in a 63% reduction in the absorption at δ 8·52. Compound (35b) was similarly obtained by reaction of *N*-4-chlorophenacylpyridinium bromide with (*E*)- or (*Z*)-dibenzoylethylene (55 and 45% yield, respectively).

1,2,4a,8a-*Tetrahydro*-3,5,8-*triphenylpyridazino*[4,5-c]*pyridazine* (37a).—A solution of the dihydrofuran (35a) (2 g, 55 mmol) and 95% hydrazine (6 ml, 0·18 mol) in ethanol (50 ml) was heated under reflux for 2 h during which time a white precipitate was deposited (1·0 g, 50%) of the *tetrahydropyridazino*[4,5-c]*pyridazine* (37a), m.p. 171—173° (Found: C, 75·2; H, 5·25; N, 13·7%; M^+, 364·1700. $C_{24}H_{20}N_4$,H_2O requires C, 75·35; H, 5·25; N, 14·3%; M, 364·1688); $\nu_{max.}$ (CHCl$_3$) 3300 cm^{-1} (NH); δ(CDCl$_3$) 4·0 (2H, s, 4a- and 8a-H), 5·4 (2H, s, D_2O exchangeable, NH), and 7—8 (16H, m, ArH). Compound (37b) was prepared in the same manner.

3,5,8-*Triphenylpyridazino*[4,5-c]*pyridazine* (38a).—A solution of the tetrahydropyridazinopyridazine (37a) (0·708 g, 2 mmol) and *p*-chloranil (1·5 g, 6 mmol) in toluene (50 ml) was heated under reflux for 18 h. Chromatography of the product on B.D.H. alumina with benzene as eluant afforded the *pyridazinopyridazine* (38a) (0·2 g, 29%) as a yellow oil (Found: M^+, 360·1370. $C_{24}H_{16}N_4$ requires M, 360·1375); $\nu_{max.}$ (CHCl$_3$) 1400 cm^{-1} (CH).

This research was supported by the National Research Council of Canada and the Chemistry Department of the University of Alberta.

[4/2545 *Received*, 7*th December*, 1974]