Reactions of Functionalized 1,3-Dipoles

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A new synthetic approach to the formation of 5–5, 5–6, 5–5–5, and 6–5–6 fused heterocycles employing cycloadditions with functionalized dipoles is described and its scope and utility explored through representative examples. The regiochemistry and stereochemistry of the additions is established by specific deuterium labelling, n.m.r. spectroscopy, and by chemical means.

On décrit une nouvelle approche synthétique à la formation des hétérocycles condensés 5–5, 5–6, 5–5–5 et 6–5–6; la généralité et l'utilité de cette méthode impliquant des cycloadditions de dipoles fonctionnalisés est examiné par l'intermédiaire d'exemples représentatifs. La régiosélectivité et la stéréochimie des additions est établie à l'aide de marquage par le deutérium de façon spécifique, par r.m.n. et par des moyens chimiques. [Traduit par le journal]

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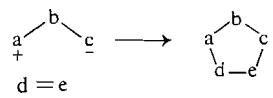
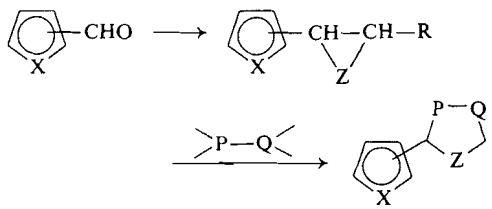
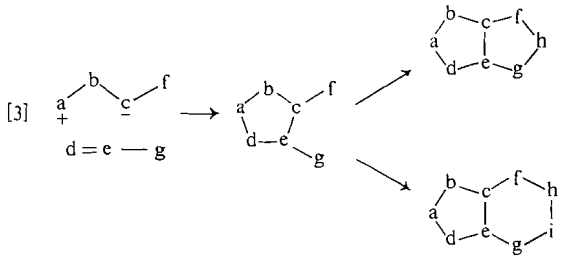
The general 1,3-dipolar addition reaction developed and systematized by Huisgen (1) and illustrated in eq. 1 is of considerable utility for the rational synthesis of a wide variety of monocyclic heterocycles. We previously extended this

[1] 

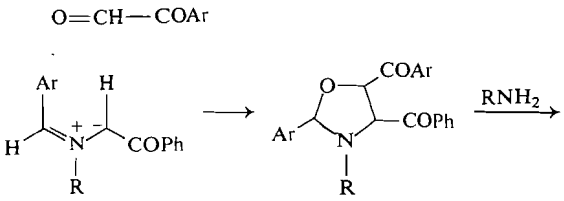
basic reaction to a scheme for the preparation of linked heterocycles (2) as illustrated in eq. 2 via consecutive condensation and 1,3-dipolar addition. A similar general synthetic scheme for the

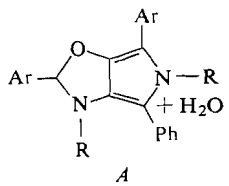
[2] 

preparation of fused ring heterocycles would be a valuable extension of the general cycloaddition principle. One approach we wish to explore in this paper is the scope of the reactions of 1,3-dipoles bearing additional functionality (*i.e.* besides their basic 4π electron reactive system) to form bicyclic heterocycles, as shown in eq. 3. The additional functionalities f and g on the 1,3-dipole and dipolarophile, respectively, should give the potential second fused five- or six-membered ring provided the reaction has the desired regiochemistry and stereochemistry. Indications of the usefulness of this approach had been obtained during an examination of the

[3] 

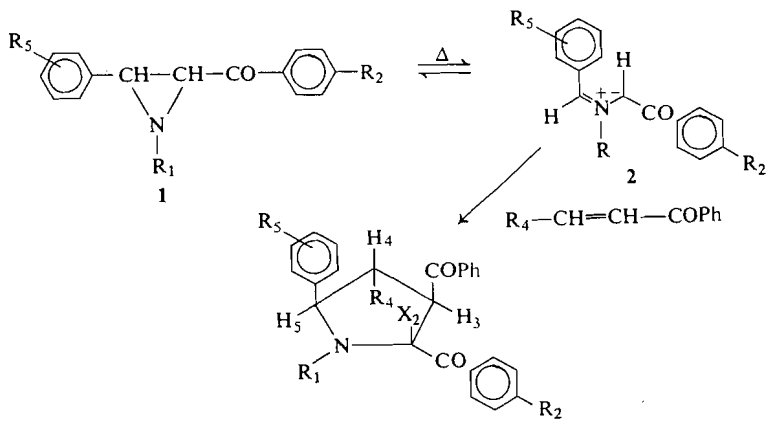
thermal decomposition of 3-aroylaziridines in acetonitrile (3, 4) and in their reaction with *p*-nitrosophenols (4) when 3,5-dihydro-2*H*-pyrrolo[3,4-*d*]oxazoles were obtained in good yield.





A

Our initial approach to systematize these findings has been to examine the reaction of aroylazomethine ylides (generated by the thermal electrocyclic cleavage of aziridines) with a range of suitably functionalized dipolarophiles). Exploratory reactions of azomethine oxides (nitrones) are also discussed in this context.



a	$R_1 = C_6H_{11}$;	$R_2 = OCH_3$;	$R_4 = mNO_2C_6H_4$;	$R_5 = H$;	$X_2 = H$
b	$R_1 = C_6H_{11}$;	$R_2 = OCH_3$;	$R_4 = C_6H_5$;	$R_5 = H$;	$X_2 = H$
c	$R_1 = C_6H_{11}$;	$R_2 = H$;	$R_4 = mNO_2C_6H_4$;	$R_5 = H$;	$X_2 = H$
d	$R_1 = (CH_3)_2CH—$;	$R_2 = H$;	$R_4 = mNO_2C_6H_4$;	$R_5 = mNO_2$;	$X_2 = H$
e	$R_1 = (CH_3)_2CH—$;	$R_2 = H$;	$R_4 = mNO_2C_6H_4$;	$R_5 = mNO_2$;	$X_2 = D$
f	$R_1 = (CH_3)_2CH—$;	$R_2 = H$;	$R_4 = pOCH_3C_6H_4$;	$R_5 = mNO_2$;	$X_2 = H$
g	$R_1 = (CH_3)_2CH—$;	$R_2 = H$;	$R_4 = C_6H_5$;	$R_5 = mNO_2$;	$X_2 = H$

SCHEME 1

Aroylazomethine Ylides and Aroylalkenes (Chalcones)

Regiochemistry of the Additions

Reaction of aziridine (**1***a*) with chalcone (**2***a*) in refluxing toluene afforded pyrrolidine (**3***a*) in 50% yield. The n.m.r. spectra of the pyrrolidines **1***a–g* showed the expected ABCD pattern for the methine protons, the chemical shifts and coupling constants of which were obtained by double irradiation experiments (see Table 1). These assignments received confirmation by a parallel experiment with specifically 3-deuterium labelled aziridine (5) (**1***e*). The n.m.r. methine pattern of the corresponding pyrrolidine (**3***e*) showed the 5.58 δ signal diminished (H_2) and the 4.01 δ signal simplified to a doublet confirming its assignment as H_3. The previous double irradiation experiments therefore confirmed 3.73 δ as H_4 and 5.15 δ as H_5.

Potassium carbonate catalyzed exchange of pyrrolidine (**3***a*) with deuterium oxide provided added confirmation in that the 4.01 δ (H_3) (α to a carbonyl group) was completely exchanged. As expected the 5.46 doublet became a singlet (H_2) after the exchange while the H_4 and H_5 signals were simplified to an AB quartet centered at 3.59 and 4.99, $J = 4$ Hz by this process. The preferential base catalyzed deuterium exchange of H_3 is characteristic of these pyrrolidines (8) (see also later examples).

The regiochemistry of the 1,3-dipolar additions indicated by the double resonance and deuterium labelling experiments received chemical confirmation by the cyclodehydration of (**3***c*) with polyphosphoric acid to the dihydrofuro-[3,4-*b*]pyrrole **4**, illustrating the potential for the synthesis of fused heterocycles, as shown in Scheme 2. All the 2,3-dibenzoylpyrrolidines gave mass spectral parent peaks of ($M - H_2O$) *i.e.* of ready loss of water to form the fused furan structure in the ion beam.

Stereochemistry of the Additions

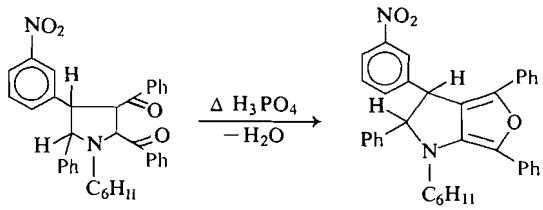
It was necessary to establish the stereochemistry of the additions so that the relative positions of the reactive groupings at C_2 and C_3 may be known since this will dictate the method to be selected in constructing a fused six-membered ring.

Stereochemical assignment of the cycloadducts was made on the basis of chemical evidence in conjunction with p.m.r. spectroscopy; the observed coupling constants are consistent with the Karplus correlation (7) and with other model pyrrolidines (6).

Previous experience in the electrocyclic conrotatory generation of azomethine ylides from 3-aroylaziridines has established that the stereoisomeric azomethine ylides equilibrate to the more stable *trans* form prior to cycloadditon (8).

TABLE 1. Double irradiation experiments on pyrrolidines at 100 MHz

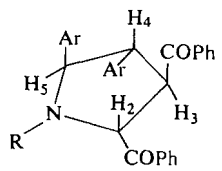
Compound	Proton irradiated	Decoupling frequency (Hz)	Lines collapsed: Original form	Lines collapsed: Final form	Measured remaining coupling (Hz)
3*b*	H_4	337	d 4.95(H_5)	s	—
	H_3	403	t 3.25(H_4)	d	J_{45} = 8.4
	H_3	403	d 5.66(H_2)	s	J_{34} = 7.5
	H_5	506	t 3.25(H_4)	d	J_{34} = 7.5
	H_2	576	d of d 3.96(H_3)	d	J_{23} = 3.4
5*A*	H_4	424	d of d 4.50(H_3)	d	J_{23} = 2.0
	H_4	424	d 5.05(H_5)	s	—
	H_3	454	d of d 4.19(H_4)	d	J_{45} = 5.0
	H_3	454	d 5.54(H_2)	s	J_{45} = 5.0
	H_5	511	d of d 4.19(H_4)	d	J_{34} = 3.5
	H_2	559	d of d 4.50(H_3)	d	J_{34} = 3.5
3*a*	H_5	509	t 3.68(H_4)	d	J_{34} = 7.5
	H_2	561	d of d 4.01(H_3)	d	J_{23} = 3.2
3*d*	H_4	316	d 5.15(H_5)	s	—
	H_3	405	d 5.58(H_2)	s	—
	H_5	519	t 3.73(H_4)	d	J_{43} = 6.5
	H_2	562	d of d 4.01(H_3)	d	J_{23} = 3.5



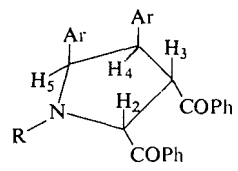
3*c* 4

SCHEME 2

This combined with the *trans* geometry of the chalcones and the known regiochemistry provides for only two possible geometries **3***A* or **3***B*.



3*A*

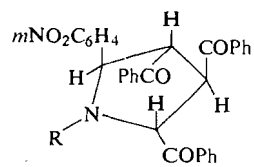


3*B*

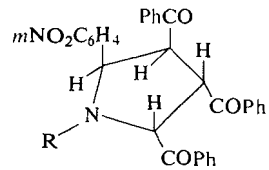
The vicinal coupling constants determined from double irradiation are J_{23} = 3, J_{34} = 7.5, and J_{45} = 8.4 Hz. Other model pyrrolidines formed by reaction with *trans*-dibenzoylethylene (see below) in which J_{23} = 7 Hz was assigned a *cis* geometry because of the rapid and characteristic condensation with hydrazine to form fused dihydropyridazine structures. The lack of reaction of the pyrrolidines obtained in the present case combined with a J_{23} = 3 Hz established the *trans–trans–trans* structure **3***A* as the correct stereoisomer. The failure to epimerize upon treatment with sodium methoxide in methanol despite the rapid deuterium exchange indicates this is also the most stable stereoisomer.

Aroylazomethine Ylides with trans-Dibenzoylethylene

Reaction of aziridines with *trans*-dibenzoylethylene afforded two stereoisomeric pyrrolidines (**5***A* and *B*) which were separable by column



5*A*

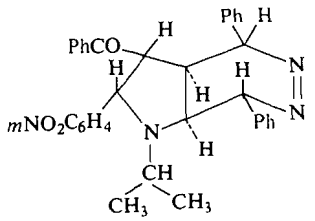


5*B*

a R = C_6H_{11}
b R = $(CH_3)_2CH$–

chromatography and recrystallization. One isomer shows an n.m.r. coupling constant of J_{23} = 7 Hz signifying a *cis* vicinal coupling in the *cis–trans–cis* structure (**5***B*). The second isomer displays a J_{23} = 2 Hz which is ascribed the *trans–trans–trans* structure (**5***A*). These assignments were confirmed chemically when pyrrolidine **5***B*, having the required *cis* arrangement for

the 2- and 3-benzoyl groups, reacted readily with hydrazine to form **6**. Both the mass spectrum and n.m.r. spectrum confirmed a composition of $C_{34}H_{32}N_4O_3$, *i.e.* corresponding to the addition of two hydrogens to the primary condensation product **7**. Since excess hydrazine was used in



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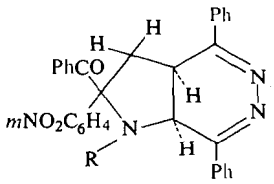

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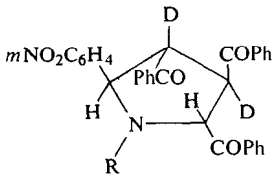
the reaction and since no NH absorption may be detected in the i.r. spectrum this indicates that the initial product **7** is further subject to a 1,4 reduction by hydrazine to give **6**. The stereoisomeric pyrrolidine **5***a*, having benzoyl groups in an all *trans* arrangement as expected failed to react with hydrazine.

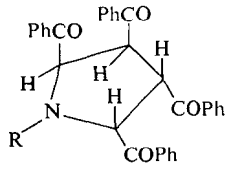
Potassium carbonate catalyzed exchange with deuterium oxide resulted in the complete exchange of protons H_3 and H_4 only, when H_2 became a singlet at 5.58 and H_5 became a singlet



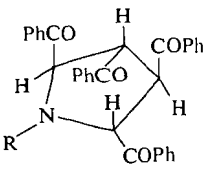
a R = C_6H_{11}
b R = $(CH_3)_2CH$—

5*c*

at 5.12 δ. Symmetrical 2,3-dibenzoylaziridines reacted with *trans*-dibenzoylethylene to give pyrrolidines **8***a* and *b*. In the case of **8***a* a single stereoisomeric pyrrolidine is obtained and assigned the *cis–trans–cis* stereochemistry (**8***aB*) since treatment with excess of hydrazine afforded **9**. In the case of **8***b* two stereoisomeric pyrrolidines were obtained, the major form of which, m.p. 183°, was assigned the



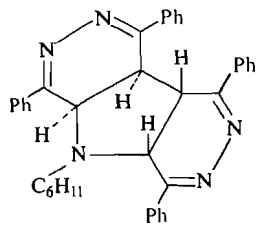
8*A*



8*B*

a R = C_6H_{11}
b R = $CH_2C_6H_5$

cis–trans–cis stereochemistry because of the close similarity of the n.m.r. spectrum with that of **8***aB*, and the second minor isomer was ascribed the *trans–trans–trans* structure (**8***bA*). Treatment of the 2,3,4,5-tetrabenzoyl-1-benzylpyrrolidine with cyclohexylamine in methanol gave the tetraphenyldipyrrolo-[3,4-*b*:3′,4′-*d*]pyrrole (**10**) in 87% yield (4).



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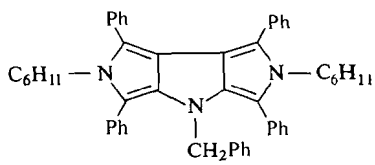
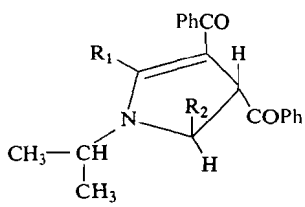


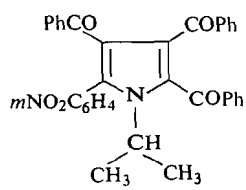
10

Aroylazomethine Ylides and Aroylalkynes

Aziridine **1***d* reacts with dibenzoylacetylene to give pyrroline **11***a* and (when the reaction is not carried out under nitrogen) some of the corresponding pyrrole **12**. Structure **11***a* is

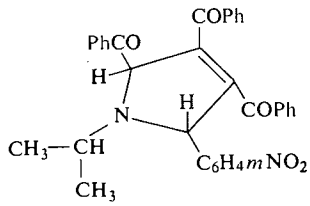


11



12

a R_1 = COPh, R_2 = $mNO_2C_6H_4$
b R_1 = $mNO_2C_6H_4$, R_2 = COPh

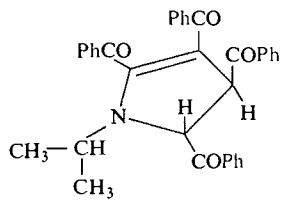


13

Ar = $mNO_2C_6H_4$

favored over the alternative 3-pyrroline form (**13**) since the compound is recovered unchanged after treatment with sodium methoxide in methanol indicating it is the more stable isomer (6). The isomeric 2-pyrroline structure **11***b* was also discounted because (*a*) the methine *trans* coupling constant 2.5 Hz is consistent with those found in analogous structures (6); (*b*) of the failure of an attempted Paal–Knorr reaction with cyclohexylamine in contrast to *e.g.* **3***c*, **8***b*; and (*c*) the position of the isopropyl methine 3.70 δ is also consistent with a 2-pyrroline structure, since the corresponding position for a 3-pyrroline *N*-isopropyl methine is found to be *ca.* 3 p.p.m. (2).

Although the n.m.r. spectrum of **11** shows a singlet for the methine protons at 4.93 δ, application of the Europium shift reagent resulted in the selective diamagnetic shift of one methine so that an AB pattern centered at 6.45 and 5.30 p.p.m., J = 2.5 Hz, resulted. This selective shift suggests the methines are in substantially different environments favoring pyrroline **11** over pyrroline **13** (*N.B.* contrast example **14**). The evident preference for formation of the 2-pyrroline isomer during cycloaddition is indicated by reaction of 1-isopropyl-2,3-dibenzoylaziridine with dibenzoylacetylene to form **14**. The structural assignment is supported by its lack of isomerization with sodium methoxide in methanol ruling out a 3-pyrroline structure (6) even though the methines appear as a singlet at 6.20 δ. Application of the Europium shift reagent resulted in complexing to the 4,5-carbonyls with a resultant shift of the methines *as a singlet* to δ 6.84. This result, in contrast to the previous case, points to the methines being in a closely similar chemical environment.



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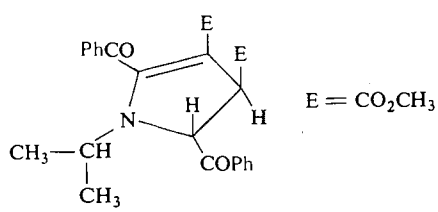
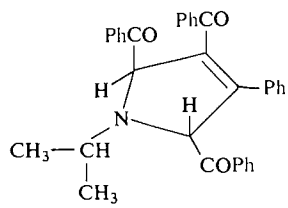


15

Another indication of the 2-pyrroline form is the characteristic position of the isopropyl methine at 4.25 δ. A similar formation of a 2-pyrroline is observed in the reaction of the same aziridine with dimethyl acetylenedicarboxylate to give pyrroline **15**. In the reaction of 1-isopropyl-2,3-dibenzoylaziridine with 1,3-diphenylpropynone preferential formation of the kinetically controlled cycloaddition product, the 3-pyrroline **16** was observed. Treatment of **16**



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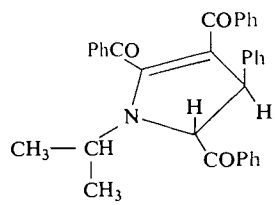
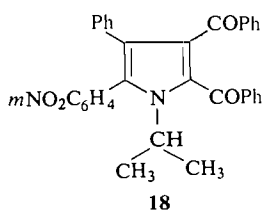


17

with sodium methoxide in methanol resulted in isomerization to the more stable 2-pyrroline **17**, assigned the *trans* geometry since the methines appeared as singlets. The question of the regiochemistry of unsymmetrical acetylenic dipolarophiles could be determined by examining the reaction of aziridine **1***d* with benzoylstyrene. In this case the initially formed pyrroline is oxidized *in situ* to the pyrrole **18**. The latter was related



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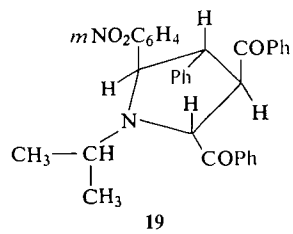
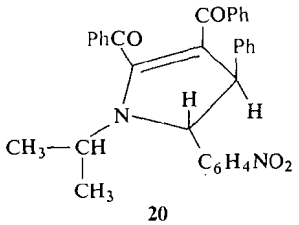


19

structurally to the corresponding chalcone adduct **19**, the regiochemistry and stereochemistry of which has previously been established. Controlled dehydrogenation of pyrrolidine **19** with *p*-chloranil (9) gave initially the pyrroline **20**. Further treatment of compound **20** with *p*-

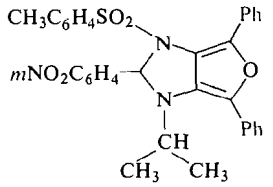


20

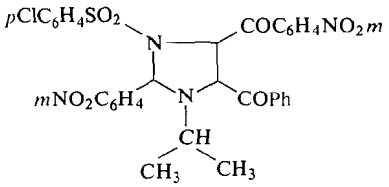
chloranil gave the pyrrole **18** obtained from benzoylstyrene.

Aroylazomethine Ylides with Imidodipolarophiles

Imine dipolarophiles are not normally very reactive, however when polarized by an adjacent group, say arylsulfonyl, we have found their 1,3-dipolar reactivity to be substantially enhanced (5). Thus reaction of aziridine **1***d* with the benzoylsulfonylimine gave the fused bicyclic structure **21** formed by spontaneous Paal–Knorr ring



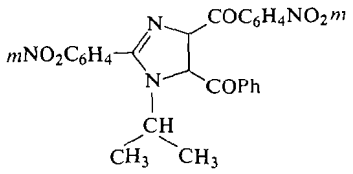
21



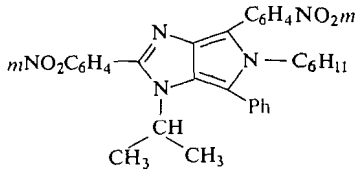
22

closure of the initially formed imidazolidine and the accompanying generation of water results in some hydrolysis of the sulfonylimine to the *p*-toluenesulfonamide.

Reaction of aziridine **1***d* with the *m*-nitrobenzoylsulfonylimine took a different course in that the product imidazolidine **22** had not cyclized but had suffered a partial base-catalyzed elimination of the arylsulfinic acid group, so the 2-imidazoline **23** is isolated as well.



23

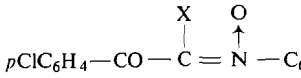


24

The regiochemistry of the addition and proposed structure of the imidazoline **21** was confirmed by the facile Paal–Knorr reaction with cyclohexylamine to give compound **22**. It may be noted that in the formation of fused heterocycles (*e.g.* **A**, **21**, **24**, **27**) by Paal–Knorr condensation, the reactions are considerably facilitated by having heteroatoms or other strongly polarizing groups adjacent to both aroyl groups. This is further exemplified in the following reactions with functionalized azomethine oxides. A second analogous set of examples is described in the Experimental section.

Aroylazomethineoxides with Dibenzoylethylene

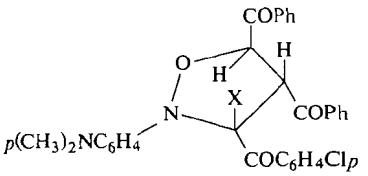
The nitrone **25***a* readily underwent reaction with *trans*-dibenzoylethylene to give the isoxazolidine **26***a*. Paal–Knorr condensation took place



a X = H
b X = D

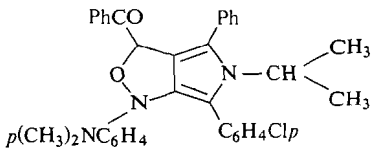
25

readily with isopropylamine to give the fused heterocycle **27**. The structural ambiguity with respect to this condensation was resolved by



a X = H
b X = D

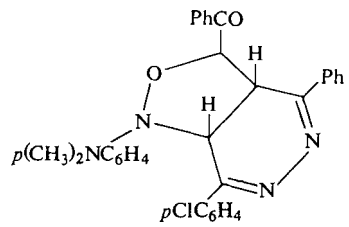
26



27

using specifically deuterium labelled nitrone **25***b* which reacted with *trans*-dibenzoylethylene to give the 3-*d* isoxazolidine **26***b*. Since treatment with isopropylamine also gave **27**, therefore the Paal–Knorr reaction occurs at positions 3 and 4

rather than positions 4 and 5. Hydrazine reacts readily with the *cis* vicinal aroyl groups of the isoxazolidine **26** (necessarily at positions 3 and 4) to give compound **28**. The representative ex-



28

amples discussed in this paper serve to illustrate the potential of this approach towards a general synthesis of fused heterocycles. At present the principal limitation appears to be one of yield in many cases. However this is compensated for by the experimental convenience and simplicity and the accessibility of the starting materials.

Experimental

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The i.r. spectra were recorded on a Perkin-Elmer model 421 spectrophotometer and only the principal, sharply defined peaks are reported. The n.m.r. spectra were recorded on Varian A-60 and A-100 analytical spectrometers. The spectra were measured on approximately 10–15% (w/v) solutions in $CDCl_3$, with tetramethylsilane as a standard. Line positions are reported in p.p.m. from the reference. Mass spectra were determined on an Associated Electrical Industries MS-9 double focusing high resolution mass spectrometer. The ionization energy, in general, was 70 eV. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15 000. Kieselgel DF-5 (Camag, Switzerland) and Eastman Kodak precoated sheets were used for t.l.c. Microanalyses were carried out by Mrs. D. Mahlow of this department.

Materials

(a) General Preparation of 3-Aroylaziridines

These compounds were prepared by established methods involving Aldol condensations to form chalcones followed by bromination to afford dibromochalcones and finally, treatment with primary amines to afford the aroylaziridines (10).

(b) Preparation of Aroyl N-Sulfonylimines

(*i*) *m*-Nitrophenylglyoxal methyl acetal was prepared by the method of Claisen (11) in 87% yield, b.p. 120°/2 mm (lit. b.p. 145–146°/9 mm).

(*ii*) The preparation of *N*-(*m*-nitrophenylglyoxal)-*p*-toluenesulfonamide is typical of the preparation of other aroyl *N*-sulfonylimines and the procedure is due to Kresze and co-workers (12).

A mixture of 7.30 g (32 mmol) of *m*-nitrophenylglyoxalmethyl acetal and 5.56 g (32.5 mmol) of *p*-toluenesulfonamide was heated with stirring to 150° for 1 h during which time methanol was evolved. Upon cooling the residual oil solidified and the product was purified by recrystallization from toluene–dioxan, m.p. 205–208°, 5.5 g (53% yield).

Anal. Calcd. for $C_{15}H_{12}N_2O_5S$ (mol. wt. 332.26): C, 54.22, H, 3.64; N, 8.43. Found (332, mass spectrum): C, 54.44; H, 4.3; N, 8.21.

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.32 (3H, s, CH_3); 6.25 (1H, s, methine); 7–9 (8H, m, aryl protons).

(c) Preparation of Nitrones

N-Benzoylmethylene-4-dimethylaminoaniline-*N*-oxide and similar nitrones were prepared by the procedure of Krohnke and Borner (13) and in this case yield 55%, m.p. 109–111° (lit. (13) m.p. 110–111°).

Cycloadditions of Aroylazomethine Ylides with Chalcones

(a) Reaction of 3-p-Anisoyl-1-cyclohexyl-2-phenylaziridine with 3-m-Nitrophenyl-1-phenyl-2-propen-1-one

This reaction is typical of a series of six reactions of 3-aroylaziridines with chalcones to form pyrrolidines which are summarized in Table 2. A solution of 3.35 g (10 mmol) of the aziridine and 2.53 g (10 mmol) of the chalcone in 50 ml of benzene was heated under reflux for 12 h. The solvent was removed *in vacuo* and the residual oil subjected to chromatography on 100 g of B.D.H. grade I alumina with benzene eluant. The first fraction upon concentration gave pyrrolidine **3***a* purified by recrystallization from hexane–benzene, m.p. 140–142° 2.90 g, (50% yield).

Mol. Wt. Calcd. for $C_{37}H_{36}N_2O_5$: 588.2624. Found (mass spectrum): 588.2630.

The i.r. spectrum ν_{max} ($CHCl_3$): 1670 cm^{-1} (C=O). The n.m.r. spectrum TMS ($CDCl_3$): 3.62 (1H, t, J_{34} = 7.5 Hz, J_{23} = 3 Hz, H_3); 5.05 (1H, d, J_{45} = 8.4 Hz, H_5); 5.66 (1H, d, J_{23} = 3.0 Hz, H_2).

Double irradiation experiments are summarized in Table 1. Pyrrolidine **3***a* (0.1 g) was subjected to deuterium exchange by heating under reflux in a mixture of 10 ml anhydrous dioxan and 10 ml of deuterium oxide with 0.1 g of potassium carbonate. The n.m.r. spectrum showed almost complete exchange of the proton giving rise to the 4.01 δ doublet of doublets and ascribed to H_3 (see Table 2).

(b) Reaction of 3-Benzoyl-3-deuterio-1-isopropyl-2-m-nitrophenylaziridine with 3-m-Nitrophenyl-1-phenyl-2-propen-1-one

A solution of 1.48 g, (4.8 mmol) of the deuterated (or undeuterated) aziridine and 1.26 g (4.9 mmol) of the chalcone in 50 ml of toluene was heated under reflux overnight, then the usual work-up procedure afforded pyrrolidine (**3***e*), 2.0 g (72% yield), m.p. 131–133° (CH_3OH).

Anal. Calcd. for $C_{33}H_{29}N_3O_6$ (mol. wt. 563.2056): C, 70.32; H, 5.19; N, 7.46. Found (563.2070, mass spectrum): C, 69.58; H, 5.05; N, 7.55.

The i.r. spectrum ν_{max} ($CHCl_3$) 1670 cm^{-1}. The n.m.r. spectrum δ TMS ($CDCl_3$), 0.9 (6H, d of d, J = 6 Hz; $(CH_3)_2CH$); 3.0 (1H, m, $(CH_3)_2CH$); 4.01 (1H, d of d, J_{23} = 6.5, 3.0 Hz, H_3); 5.15 (1H, d, J = 8.5 Hz, H_5); 5.58 (1H, d, J = 3.5 Hz, H_2). The n.m.r. spectrum of the deuterated sample showed the doublet at 5.58 δ is diminished in intensity (therefore H-2) and the quartet at 4.01 δ became a doublet (J = 6.5 Hz) (therefore H_3).

(c) Paal–Knorr Reaction with 1-Cyclohexyl-2,3-dibenzoyl-4-m-nitrophenyl-5-phenylpyrrolidine. Formation of a Furo[3,4-b]pyrrole

1-Cyclohexyl-2,3-dibenzoyl-4-*m*-nitrophenyl-5-phenyl-

TABLE 2. Pyrrolidines

No.	Melting point (°C)	Yield (%)	Found C	Found H	Found N	Found Molecular ion (mass spectrum	Calculated C	Calculated H	Calculated N	Calculated Molecular ion (mass spectrum)	Nuclear magnetic resonance spectrum (methines) H_2	H_3	H_4	H_5	J_{23}	J_{34}	J_{45}	Infrared spectrum ($CHCl_3$) C=O
3*a*[a]	140–142	50	—	—	—	588.2635	—	—	—	588.2624	5.66d	4.01q	3.68t	5.05d	3.0	7.5	8.4	1670
3*b*[a]	Oil	62	—	—	—	543.2770	—	—	—	543.2773	5.66d	3.96q	3.25t	4.95d	3.4	7.5	8.3	1665
3*c*	176–178	83	79.86	5.99	5.20	558.2520	79.93	5.95	5.17	558.2518	5.51d	3.92q	3.62t	4.99d	3.0	7.0	8.0	1670
3*d*	131–133	72	69.58	5.05	7.55	563.2070	70.32	5.19	7.46	563.2056	5.58d	4.01q	3.73t	5.15d	3.0	6.5	8.5	1670
3*f*	138–139	25	74.14	5.86	5.10	548.2506	74.43	5.88	5.11	548.2510	5.75d	3.99q	3.17t	5.08d	3.0	7.0	8.0	1665
3*g*	Oil	52	—	—	—	518.2201	—	—	—	518.2205	5.75d	4.02q	3.39t	5.12d	3.5	7.5	8.0	1670
5*Ab*	128–130	56	74.64	5.53	5.31	546.2161	74.71	5.53	5.13	546.2153	5.50d	4.50q	4.29q	5.09d	2.0	3.5	5.0	1662
5*Aa*	Oil	10	—	—	—	481(—COPh)	—	—	—	585	5.54d	4.50q	4.19q	5.05d	2.0	3.5	5.0	1660
5*Bb*	198–199	16	74.36	5.29	5.18	546.2159	74.36	5.29	5.18	546.2153	5.65d	5.19q	5.19q	5.29d	8.0	1.5	7.0	1660
5*Ba*	183–185	48	75.59	5.92	4.77	481.2120 (—COPh)	75.75	5.84	4.78	481.2126	5.58d	5.19q	4.99q	5.31d	7.5	1.5	6.5	1660
8*Aa*	228–230	62	79.77	6.15	2.77	464.2220 (—COPh)	80.11	6.19	2.76	464.2226	—multiplet—		(5.15–5.78)		—	—	—	1670

[a]Decomposes rapidly in light or air.

TABLE 3. Pyrrolines and pyrroles

No.	Melting point (°C)	Yield (%)	Found C	Found H	Found N	Found Molecular ion (mass spectrum)	Calculated C	Calculated H	Calculated N	Calculated Molecular ion (mass spectrum)	Nuclear magnetic resonance spectrum (methines) H_4	H_5	J_{45}	R1 Methine	Infrared spectrum ($CHCl_3$) C=O
11	183–184	56	74.80	5.20	5.80	544.1992	74.98	5.18	5.14	544.1998	4.93(s) 6.45d, with Eu agent	5.30d	2.5	3.68	1660
12	Oil	35	—	—	—	542.1841	—	—	—	542.1832	—		—	4.58	1645
14	201–203	60	79.57	5.48	2.61	527.2090	79.67	5.54	2.66	527.2096		6.20(s)	—	4.20	1660
15	196–197	58	68.65	5.55	3.14	435.1671	68.95	5.79	3.22	435.1682		4.48(m)[a]	—	4.20	1665 1735
16	132–134	36	81.48	5.81	3.01	499.2159	81.74	5.85	2.80	499.2147	6.21(d)	6.52(d)	3.5[d]	3.35	1662
17	Oil	46	—	—	—	499.2150	—	—	—	499.2147	4.30(d)	5.25(d)	7.0	3.62	1660
18[c]	189–190	77	76.92	5.05	5.31	514.1901	77.02	5.09	5.44	514.1893	—		—	4.50	1630
20	140–141	80	75.97	5.47	5.52	516.2062	76.72	5.46	5.42	516.2049	4.40(d)	4.86(d)	5.0	3.60	1660
3c[b]	Oil	76	—	—	—	556.2370	—	—	—	565.2361	4.52(d)	4.79(d)	5.0	3.62	1662

[a] H_6 not evident, apparently obscured by aromatic protons.
[b] Obtained from dehydrogenation of the corresponding pyrrolidine.
[c] Obtained as oxidation product from cycloaddition of aziridine and alkene.
[d] J_{25}.

pyrrolidine (0.4 g, 7.2 mmol) was heated with 20 ml of polyphosphoric acid at 150° for 2 h. The reaction mixture was poured into ice water, extracted with benzene, and the benzene extract dried (Na_2SO_4). Removal of the solvents *in vacuo* gave 4-cyclohexyl-5,6-dihydro-6-*m*-nitrophenyl-4*H*-furo[3,4-*b*]pyrrole (4), 0.11 g (30% yield).

Mol. Wt. Calcd. for $C_{36}H_{32}N_2O_3$: (540.2413). Found (mass spectrum): 540.2419.

The n.m.r. spectrum δ TMS ($CDCl_3$): 4.35 (1H, d, J_{56} = 5.0 Hz, H_5), 4.95 (1H, d, J_{56} = 5.0 Hz, H_6).

Reaction of 3-Benzoyl-1-isopropyl-2-m-nitrophenylaziridine with trans-Dibenzoylethylene

A solution of 1.48 g (5 mmol) of the aziridine and 1.18 g (5 mmol) of *trans*-dibenzoylethylene in 50 ml of benzene was heated under reflux overnight. Monitoring of the reaction by t.l.c. (silica gel – benzene) showed the presence of two products. Removal of the solvent *in vacuo* and trituration of the residual oil with methanol gave a first crop of yellow crystals 0.43 g (16% yield) m.p. 198–199°. Concentration of the mother liquor afforded a second crop 1.50 g (56% yield) m.p. 128–130°. The stereoisomeric pyrrolidines **5***A* and *B* could also be separated by column chromatography (B.D.H. alumina–benzene) when the lower melting isomer was eluted first. This isomer was assigned the structure and stereochemistry **5***A* *i.e.* *trans–trans–trans*-1-isopropyl-5-*m*-nitrophenyl-2,3,4-tribenzoylpyrrolidine based on the n.m.r. spectrum (see Table 2) and on the double irradiation experiments performed on a close analog (*i.e.*, *N*-substituent is cyclohexyl rather than isopropyl) (see Table 3).

The higher melting stereoisomer was assigned the *cis–trans–cis* structure **5***B* based upon its chemical reactivity towards hydrazine and upon its n.m.r. spectrum which shows two characteristically larger *cis* vicinal couplings of J = 6 and 7 Hz, respectively, for the methine absorptions.

Base Catalyzed Deuterium Exchange of trans–trans–trans-1-Isopropyl-5-m-nitrophenyl-2,3,4-tribenzoylpyrrolidine

A solution of 0.1 g of **5***A* and 0.1 g of potassium carbonate in 20 ml of 1:1 dioxan – deuterium oxide was heated under reflux for 2 h. Nuclear magnetic resonance examination of the recovered material showed complete exchange of H_3 and H_4 leaving H_2 and H_5 as singlets at 5.58 and 5.12 δ, respectively.

Reaction of cis–trans–cis-1-Isopropyl-5-m-nitrophenyl-2,3,4-tribenzoylpyrrolidine with Hydrazine

A solution of 0.2 g (0.37 mmol) of pyrrolidine **5***B* and 0.5 ml of 95% hydrazine hydrate in 20 ml of methanol was heated under reflux for 1 h. Cooling resulted in precipitation of 0.11 g (55% yield) of 7-benzoyl *cis–cis–cis*-(1,4)(4a, 7a)(6,7)-hexahydro-5-isopropyl-1,4-diphenyl-6-*m*-nitrophenyl-5*H*-pyrrolo[2,3-*d*]pyridazine (**6**) m.p. 85°.

Mol. Wt. Calcd. for $C_{34}H_{32}N_4O_3$: 544.2474. Found (mass spectrum): 544.2470.

The i.r. spectrum ν_{max} ($CHCl_3$) 1660 cm^{-1} (C=O). The n.m.r. spectrum δ TMS ($CDCl_3$): (methines) 4.33 (1H, d, J = 7.5 Hz), 4.52 (1H, d, J = 7 Hz); 4.82 (2H, s,); 5.29 (1H, d, J = 5.0 Hz), 5.49 (1H, d, J = 5.5 Hz).

Reaction of 1-Cyclohexyl-2,3,4,5-tetrabenzoylpyrrolidine with Hydrazine

A solution of 0.157 g (0.266 mmol) of pyrrolidine **8***A* and 0.03 ml (0.532 mmol) of hydrazine in 20 ml of methanol was heated under reflux for 2 h during which time a precipitate formed of 5-cyclohexyl-*cis-cis*-(1a,4a)(5a,9a)-tetrahydro-1,4,6,9-tetraphenyl-5*H*-dipyridazino-[4,5-6,4′,5′-*d*]pyrrole (**9**) 0.07 g (46% yield) m.p. 85–90°.

Anal. Calcd. for $C_{38}H_{35}N_5$ (mol. wt. 561.2892): C, 81.25; H, 6.28; N, 12.47. Found (561.2906, mass spectrum): C, 81.24; H, 5.91; N, 12.28.

The i.r. spectrum ν_{max} ($CHCl_3$) 1669 cm^{-1} (C=N); n.m.r. δ TMS ($CDCl_3$): 1–2 (1H, m, C_6H_{11}), 5.2 (4H, m, methines), 7–8 (20H, m, Ar-H).

Dehydrogenation of a Pyrrolidine to a Pyrroline with High Potential Quinone

A solution of 0.518 g (1 mmol) of 2,3-dibenzoyl-1-isopropyl-5-*m*-nitrophenyl-4-phenylpyrrolidine (**3***g*) and 0.246 g (1 mmol) of *p*-chloranil in 50 ml of toluene was heated under reflux for 2 days. The solvent was removed *in vacuo* and the residue subjected to column chromatography on 20 g of B.D.H. alumina with benzene as eluant. The first fraction gave 0.05 g (10%) of unreacted pyrrolidine and the second fraction gave 2,3-dibenzoyl-1-isopropyl-5-*m*-nitrophenyl-4-phenyl-2-pyrrolidine (**20**) 0.41 g (80% yield) as an oil.

Anal. Calcd. for $C_{33}H_{28}N_2O_4$ (mol. wt. 516.2049): C, 76.73; H, 5.46; N, 5.42. Found (516.2062, mass spectrum): C, 75.97; H, 5.47; N, 5.52.

The i.r. spectrum ν_{max} ($CHCl_3$) 1660 cm^{-1}. The n.m.r. spectrum δ TMS ($CDCl_3$) 1.0 (6H, d of d, J = 7 Hz, $(CH_3)_2CH$); 3.60 (1H, m, $(CH_3)_2CH$), 4.40 (1H, d, J_{23} = 5.0 Hz, H_3); 4.86 (1H, d, J_{23} = 5.0 Hz, H_2), 7–8.5 (19H, m, ArH). When 2 equiv. of *p*-chloranil were used, pyrroline **20** in 70% yield together with a small amount of pyrrole **18** (10%) when eluted with chloroform.

Dehydrogenation of 1-Isopropyl-5-m-nitrophenyl-2,3,4-tribenzoyl-2-pyrroline with p-Chloranil

A solution of 0.54 g (1 mmol) of pyrroline **20** and 0.25 g (1 mmol) of *p*-chloranil in 20 ml of toluene was heated under reflux for 14 h (10). Column chromatography on B.D.H. alumina with 1:1 benzene–chloroform afforded the pyrrole **18** 0.35 g (30% yield) (see Table 3).

Cycloadditions of Aroylazomethine Ylides with Acetylenes. Reaction of 1-Isopropyl-2-m-nitrophenyl-3-benzylaziridine with trans-Dibenzoylacetylene

A solution of 1.66 g (7.1 mmol) of *trans*-dibenzoylacetylene and 2.20 g (7.1 mmol) of the above aziridine in 50 ml of benzene was heated under reflux for 12 h. Hexane (50 ml) was added to the hot solution which was set aside at room temperature for 2 days when crystals of 1-isopropyl-5-*m*-nitrophenyl-2,3,4-tribenzoyl-2-pyrroline (**11**) separated, 1.1 g (30% total yield) m.p. 183–184°.

Anal. Calcd. for $C_{34}H_{28}N_2O_5$ (mol. wt. 544.1998): C, 74.98; H, 5.18; N, 51.4. Found (544.1992, mass spectrum): C, 74.80; H, 5.23; N, 5.0.

The i.r. spectrum ν_{max} ($CHCl_3$) 1660 cm^{-1} (C=O). The n.m.r. spectrum δ TMS ($CDCl_3$): 1.0 (6H, d of d, $(CH_3)_2CH$—); 3.7 (1H, m, $(CH_3)_2CH$—), 4.93 (2H, s, methine), 7–8.2 (19H, m, aryl). Upon treatment with Europium shift reagent, the H_2, H_3 singlet at 4.93 became an AB quartet centered at 5.30 and 6.45 δ, J = 2.5 Hz.

Chromatography of the mother liquor on B.D.H. alumina with benzene as eluent gave a further 1.0 g of the pyrroline **11** and 1.3 g of an oil which eluted with chloroform and which crystallized from hexane as

colorless prisms, m.p. 100–101°, 1-isopropyl-5-*m*-nitrophenyl-2,3,4-tribenzoylpyrrole (**12**).

Mol. Wt. Calcd. for $C_{34}H_{26}N_2O_5$: 542.1832. Found (mass spectrum): 542.1827.

The i.r. spectrum ν_{max} ($CHCl_3$) 1645 cm^{-1} (C=O); n.m.r. δ TMS ($CDCl_3$): 1.2 (6H, d of d, J = 7 Hz, $(CH_3)_2CH$—), 4.58 (1H, m, $(CH_3)_2CH$—), 7–9 (19H, m, aryl protons).

Base Catalyzed Deuterium Exchange

A solution of 0.1 g of compound **11** and 0.1 g of potassium carbonate in 50 ml of 1:1 dioxan – deuterium oxide was heated under reflux for 2 h. Examination of the n.m.r. spectrum of the recovered 2-pyrroline showed the 4.93 singlet had diminished to 1H due to exchange of H_4. No other structural changes had occurred indicating this to be the more stable 2-pyrroline isomer.

Base Catalyzed Isomerization of a 3-Pyrroline to a 2-Pyrroline

A solution of 1 g (2 mmol) 1-isopropyl-4-phenyl-2,3,5-tribenzoyl-3-pyrroline (**16**) (prepared from 1-isopropyl-2,3-dibenzoylaziridine and 1,3-diphenylpropynone) in methanol with a trace of sodium methoxide was stirred overnight at room temperature. Removal of the solvent *in vacuo* gave a substance (**17**) isomeric with the compound **16** (*i.e.* mass spectrum 499.2156. Calcd. for $C_{34}H_{29}NO_3$: 499.2147). The n.m.r. spectrum δ TMS ($CDCl_3$) 3.6 (1H, m, $(CH_3)_2CH$—), 4.1, 5.75 (1H each, s, H_4, H_5). On this basis the compound was assigned as 1-isopropyl-4-phenyl-2,3,5-tribenzoyl-2-pyrroline (**17**).

Cycloadditions of Aroylazomethine Ylides with Aroylsulfonylimines. Reaction of 1-Isopropyl-2-m-nitrophenyl-3-benzoylaziridine with Benzoyl-N-p-toluenesulfonylimine

A solution of 2.16 g (7 mmol) of the aziridine and 2.0 g (7 mmol) of the sulfonylimine in 50 ml of benzene–dioxan (10:1) or acetonitrile was heated under reflux for 12 h and the resulting precipitate was collected representing 4,5-dibenzoyl-1-isopropyl-2-*m*-nitrophenyl-3-*p*-toluenesulfonylimidazolidine, m.p. 272–273°, 0.4 g (7% yield).

Mol. Wt. Calcd. for $C_{33}H_{28}N_3O_4S$: 562. Found (mass spectrum): 562.

The i.r. spectrum ν_{max} ($CHCl_3$): 1635, (C=O) 1160, 1330 cm^{-1} (SO_2). The n.m.r. spectrum δ TMS ($CDCl_3$): 1.33 (6H, d, J = 7 Hz, $(CH_3)_2CH$—); 2.21 (3H, s, CH_3); 3.5 (1H, m, $CH(CH_3)_3$); 7–9 (20H, m, aryl).

The mother liquor was subjected to chromatography on B.D.H. alumina with benzene as eluent which gave some unreacted aziridine (0.3 g) and a second product 4,5-dibenzoyl-1-isopropyl-2-*m*-nitrophenyl-2-imidazoline, 0.25 g (9% yield) m.p. 205°.

Anal. Calcd. for $C_{26}H_{21}N_3O_4$ (M − 2H, 439.1532): C, 70.73: H, 5.25: N, 9.52. Found (439.1535, mass spectrum): C, 69.58; H, 4.95; N, 9.39.

The analogous 5-benzyl-3-*p*-chlorotoluenesulfonyl-1-isopropyl-4-*m*-nitrobenzoyl-2-*m*-nitrophenylimidazolidine (**22**), m.p. 278–279° and 5-benzoyl-1-isopropyl-4-*m*-nitrobenzoyl-2-*m*-nitrophenyl-2-imidazoline (**23**), m.p. 105° were prepared similarly in 12 and 20% yields, respectively.

Paal–Knorr Formation of a Pyrrolo[3,4-d]imidazole

A solution of 0.15 g of compound **23** and 1 ml of cyclohexylamine in 20 ml of methanol was heated for 1 h then set aside overnight. Chromatography of the resulting mixture on B.D.H. alumina with benzene gave 5-cyclohexyl-1,5-dihydro-2,4-di-*m*-nitrophenyl-1-isopropyl-6-phenylpyrrolo[3,4-*d*]imidazole (**24**), 0.08 g (60% yield).

Mol. Wt. Calcd. for $C_{32}H_{31}N_5O_4$: 549.2375. Found (mass spectrum): 549.2379.

The n.m.r. spectrum δ TMS ($CDCl_3$): 1.20 (10H, m cyclohexyl CH_2), 1.3 (6H, d, J = Hz, $(CH_3)_2CH$); 3.5 (2H, m, methines), 7–9 (13H, m, aryl protons).

Cycloadditions of Aroylazomethineoxides with Aroylalkenes

A solution of 1.18 g (5 mmol) of *trans*-dibenzoylethylene and 1.51 g (5 mmol) of the nitrone *N*-*p*-chlorobenzoylmethylene-4-dimethylaminoaniline-*N*-oxide in 100 ml of dry benzene was stirred overnight at room temperature. Most of the solvent was removed *in vacuo* and the resulting precipitate collected and purified by recrystallization from hexane–benzene to give 4,5-dibenzoyl-3-*p*-chlorobenzoyl-2-*p*-dimethylaminophenylisoxazolidine (**26**) 1.8 g (67% yield), m.p. 210–212°.

Paal-Knorr Formation of a Pyrrolo[3,4-c]isoxazole

(*a*) A solution of 0.2 g (3.7 mmol) of 4,5-dibenzoyl-3-*p*-chlorobenzoyl-2-*p*-dimethylaminophenylisoxazolidine (**26**) in 20 ml of methanol was treated with 2 ml of isopropylamine. A red color developed immediately and the solution was stirred overnight. Removal of the solvent *in vacuo* gave 3-benzoyl-6-*p*-chlorophenyl-3,5-dihydro-1-*p*-dimethylaminophenyl-5-isopropyl-4-phenyl-1*H*-pyrrolo-[3,4-*c*]isoxazole (**27**), 0.2 g as a red oil.

Mol. Wt. Calcd. for $C_{35}H_{32}N_3O_2Cl$: 561.2192. Found (mass spectrum): 561.2196.

The n.m.r. spectrum δ TMS ($CDCl_3$): 1.1 (3H, s, CH_3); 2.7 (3H, s, N-CH_3), 6.2–8 (20H, m, aryl H and methines).

(*b*) The assigned structure was confirmed by reacting the isoxazolidine (0.10 g) labelled with deuterium at the 3-position (75% replacement by n.m.r.) with isopropylamine to afford the same pyrrolo[3,4-*c*]isoxazole (0.1 g), (molecular ion 561, confirming loss of the label). The deuterated nitrone precursor was prepared from the pyridinium salt and *p*-nitrosodimethylamine, as before, but using CH_3OD instead of ethanol as solvent. The required deuterated acetophenone was prepared by base catalyzed deuterium exchange.

Formation of an Isoxazolo[3,4-d]pyridazine

A solution of 0.25 g (4.6 mmol) of 4,5-dibenzoyl-3-*p*-chlorobenzoyl-2-*p*-dimethylaminophenylisoxazolidine (**26**) in 10 ml of boiling ethanol was treated with 2 ml of 95% hydrazine. The solution was heated under reflux for 15 min, allowed to cool, and the yellow needles collected 0.15 g (75% yield) of 7-*p*-chlorophenyl-1-dimethylamino-phenyl-4-phenyl-3-*cis*-(3a,7a)-trihydro-1*H*-isoxazolo-[3,4-*d*]pyridazine (**28**), m.p. 269–273°.

Anal. Calcd. for $C_{32}H_{25}N_4OCl$ (M − H_2O, 516.1717): C, 71.80; Cl, 6.63. Found (516.1694, mass spectrum): C, 71.11; Cl, 6.56. (Chemical ionization mass spectrometry shows the parent peak at 534.)

The n.m.r. spectrum δ TMS ($CDCl_3$): 2.90 (6H, s, N-CH_3), 4.18 and 4.49 (2H, AB quartet, J = 9 Hz, $C_6H_4N(Me)_2$).

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