Liversidge Research Lecture

No. 27
1990

SOME NATURAL AND UNNATURAL INDOLES

DAVID St. C. BLACK

The Royal Society of New South Wales

David St Clair Black

Liversidge Research Lecturer No. 27, 1990.

DAVID ST CLAIR BLACK 1938 -

David St Clair Black was born on 22 May, 1938 at Wollongong, N.S.W. After secondary education at Wollongong High School he proceeded to the University of Sydney; in third year (1957) he was awarded the Prize for Organic Chemistry, and under the supervision of Dr. F. Lions, and with a CSIRO Junior Postgraduate Studentship (1958) he graduated B.Sc. (1st class Hons.) in 1959. He was a Teaching Fellow in the Department of Organic Chemistry in 1959-1960, and with Dr. F. Lions as supervisor, graduated M.Sc. in 1960. In 1959 he also graduated AMusA from the Sydney Conservatorium of Music. In 1960, with an Overseas Scholarship of the Royal Commission for the Exhibition of 1851, he went to Cambridge University (Christ's College) where he worked with Professor Lord Todd and Dr V.M. Clark on the application of nitrone chemistry in the synthesis of corrins, and graduated Ph.D. in 1963. During 1963-1964 he was a Postdoctoral Research Associate in Chemistry at Columbia University where he worked with Professor T.J. Katz on synthesis of non-benzenoid aromatic compounds. In 1965 he was appointed as Lecturer in Chemistry at Monash University where he was promoted to Senior Lecturer in 1971, and to Reader in 1975. In 1983 he was appointed as Professor of Organic Chemistry and Head, Department of Organic Chemistry at the University of New South Wales. For six months in 1987 he was Acting Dean, Faculty of Science, and he was Head of the School of Chemistry for the period 1987-1990. His main research interests have been in heterocyclic chemistry, including development of new synthetic methods and new aspects of indole chemistry. He has also worked on coordination chemistry, including the design and synthesis of organic ligands and the development of metal template syntheses of macrocycles. Other interests include organometallic and heterometallic anti-tumour agents and the chemistry of the endiandric acids, natural products with a novel 6,6,5,4 fused ring system. In 1992 he was Visiting Professor at the University of Aukland, and in 1994 he was an Alexander von Humboldt at Göttingen University

David Black has been involved in numerous extramural activities concerned with teaching and research in Australia and overseas. For example, he has been Indonesian coordinator for Network for the Chemistry of Biologically Important Natural Products and member of the Asian Coordinating Group for Chemistry since 1984, and he has acted as External Advisor for both the Science University of Malaysia (1986-) and the Agricultural University of Malaysia (1987-). Since 1990 he has been Chairman of the Organizing Committee for the Southern Highlands Conferences on Heterocyclic Chemistry. He was President of the Royal Australian Chemical Institute in 1998, and since 1997 has been a member (and Chair from 1997-2002) of the National Committee for Chemistry. From 2004-2011 he was Secretary General of the International Union of Pure and Applied Chemistry, and from 2011 he has been Secretary General of the International Council for Science.

Honours and Awards (Pre-2014)

1970	Rennie Medal, RACI (Royal Australian Chemical Institute)
1973	FRACI
1990	Liversidge Research Lecture, Royal Society of New South Wales
1990	Royal Society of Chemistry Lecturer in Australia.

1993	H.G. Smith Medal, RACI
2003	Birch Medal, RACI
2004	Leightom Medal, RACI
2011	Elected fellow of the Australian Academy of Science
2012	Appointed Officer of the Order of Australia

Biographical Source

Personal Communication

Scientific Publications by D.St. C. Black

Between 1965 and 2014 D.St C. Black published some 310 research papers, and he was co-author of 1 book and 6 book chapters.

Liversidge Research Lecture No. 27, 1990.

Some Natural and Unnatural Indoles*

DAVID St. C. BLACK
School of Chemistry, University of New South Wales, Kensington, N.S.W.

ABSTRACT. New reactions of specially-activated indoles provide methods by which structures related to natural products can be produced. Various 4,6-dimethoxy-substituted indoles exhibit a variety of reactions, predominantly at C7, but others at C2 or C3 instead of C7. The general increase in nucleophilic character of these indoles allows the discovery of reactions which have not been observed for other indoles. These reactions include electrophilic substitution, and addition to aldehydes and ketones. Tri-indolyl macrocycles, pyrrolo[a]indoles, cyclopentano[b]indoles and indolocarbazoles can be produced. Furthermore, new ring-fused indoles can be prepared by intramolecular nitrone 1,3-dipolar cycloaddition reactions between N1 and C2 or N1 and C7. In the latter case, similar structures can be achieved by aldol-type or organometallic reactions. The use of *N*-aroylindoles enables some known pyrrolophenanthridone alkaloids and some of their unknown analogs to be synthesized effectively.

Introduction

The indole alkaloids form an enormous class of important natural products, which in many cases show potent biological activity. As a consequence of this, synthetic studies related to indoles in general and the indole alkaloids in particular continue to be explored by many groups.

Our own work has focussed on activation at C7, which has been achieved by methoxyl group substitution at C4 and C6. Not only does this substitution activate C7 in particular, but it enhances the general reactivity of the indoles, so that new reactions can be observed. Given suitable substitution patterns, reaction can occur at C7 alone, C2 and C7, N1 and C2, C2 and C3, and N1 and C7. Thus new ring-fused indoles can be formed. The main aim of our research is to establish routes to new classes of indoles, rather than to known alkaloid structures. We are especially interested in reaching structures similar to but different from the natural products. However, from time to time, our methods also enable us to achieve effective syntheses of some important indole alkaloids.

C7 Substitution

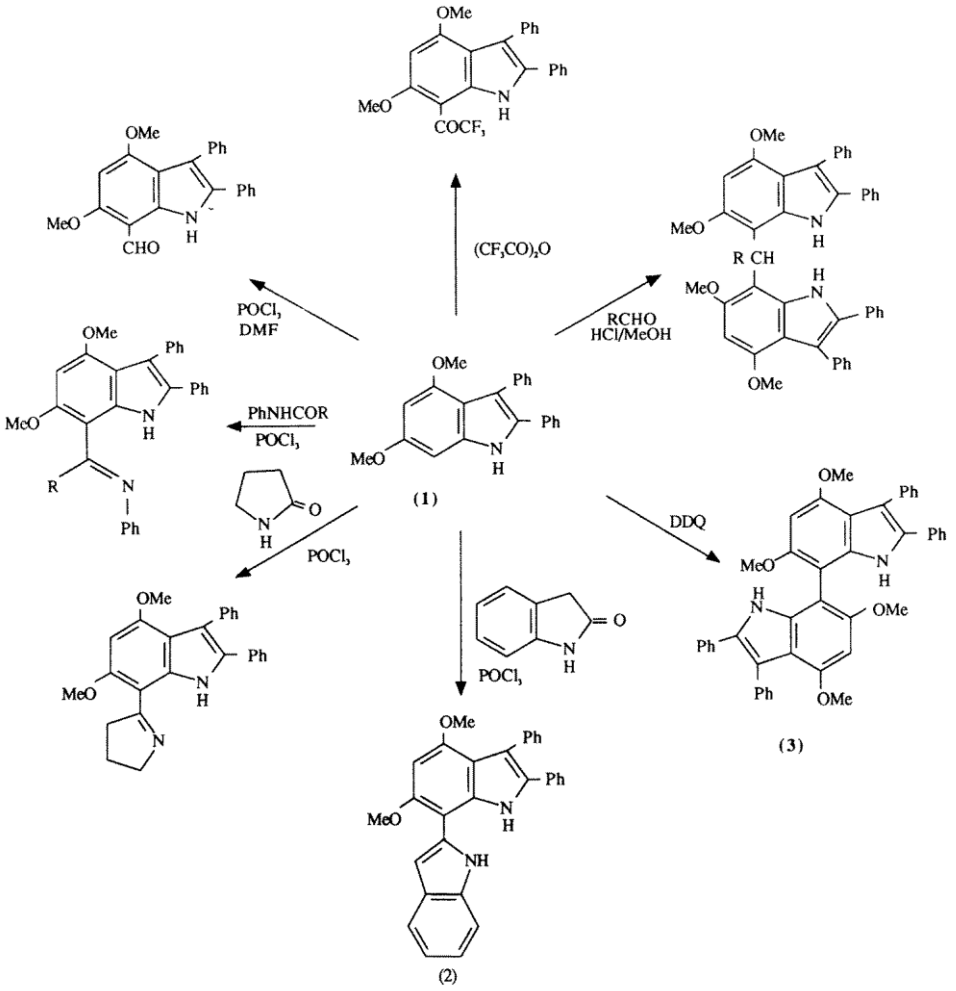
4,6-Dimethoxy-2,3-diphenylindole (1), prepared from benzoin and 3,5-dimethoxyaniline (Black *et al.*, 1986a), undergoes formylation (Black *et al.*, 1986b), acylation and acid-catalysed addition to aldehydes or ⟨,®-unsaturated ketones, all at C7 (Scheme 1). Furthermore, the Vilsmeier formylation technique can be modified to attach imines at C7. In particular, the 2,7'-bi-indolyl (2) can be prepared from indolone and phosphoryl chloride (Black and Kumar, 1994). The general reactivity of the indole (1) is such that it readily undergoes oxidative dimerisation at C7 to give the 7,7'-biindolyl (3) (Black *et al.*, 1989a).

---

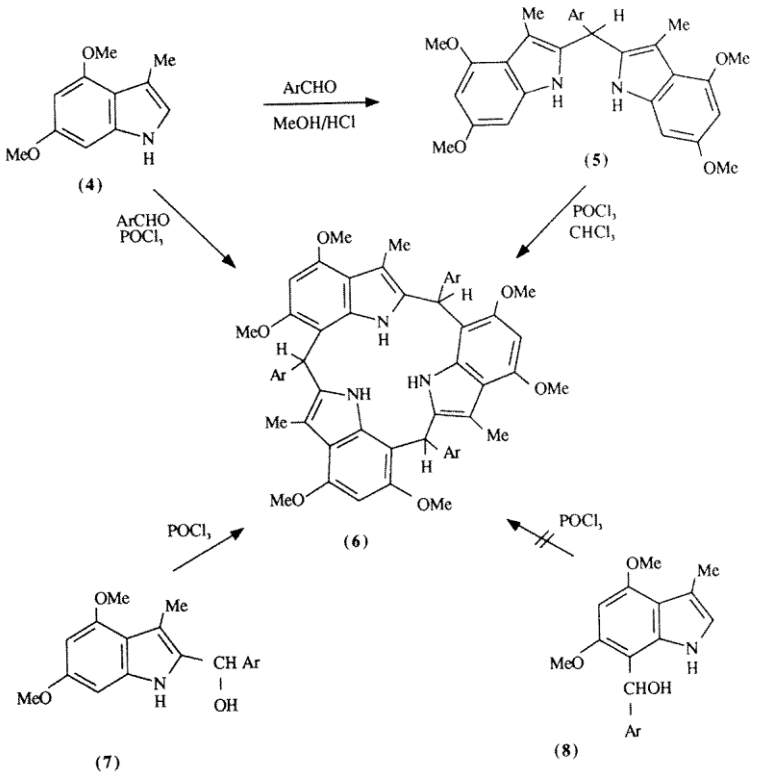
*Liversidge Research Lecture delivered before the Royal Society of New South Wales, September 5th, 1990, at the University of New South Wales. Reproduced by permission of the Royal Society of New South Wales from *J. Proc. Roy. N.S.W.*, 1990, **123**, 1-13.

C7 and C2 Substitution

In contrast to the indole (1), 4,6-dimethoxy-3-methylindole (4) (Black *et al.*, 1983) undergoes formylation at both C7 and C2. However, addition to aldehydes occurs preferentially at C2 to give 2,2'-di-indolylmethanes (5). Either these or the initial indole (4) can allow formation of a remarkable group of macrocycles (6) under conditions involving



Scheme 1



Scheme 2

phosphoryl chloride (Black *et al.*, 1989b) (Scheme 2). The parent compound (from benzaldehyde) has been shown by X-ray crystallography to have a very twisted structure, unlikely to provide any driving force for its formation (Fig. 1).

The macrocycle (6: Ar = 4Cl - Ph) can also be formed quantitatively from phosphoryl chloride and the 2-substituted alcohol (7), but not the 7-substituted alcohol (8). This implicates an intermediate which is nucleophilic at C7 and electrophilic at the C2 methyl carbon.

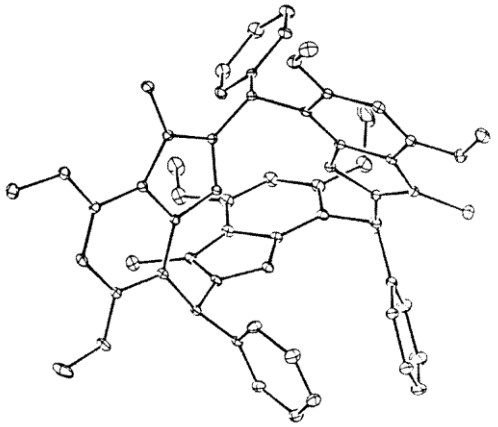


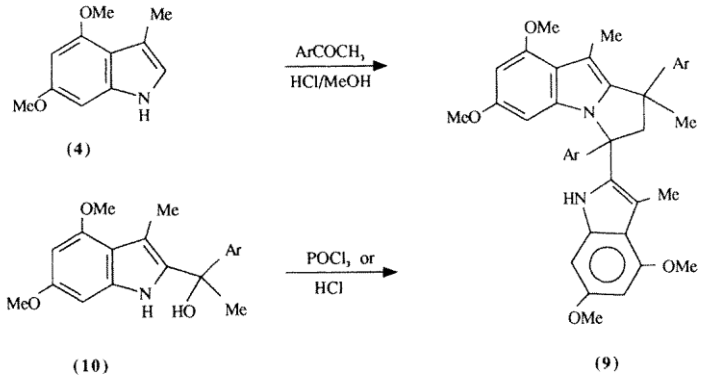
FIGURE 1. X-Ray crystal structure of macrocycle (6: Ar = Ph)

Formation of the macrocycles (6) is similar to the synthesis of porphyrins from pyrrole and aryl aldehydes. However, in the latter case, the corresponding macrocyclic tetrapyrrole

undergoes rapid oxidation to produce the highly stable aromatic porphyrin structure. A similar situation cannot arise in the case of macrocycles (6).

N1 and C2 Substitution; C2 and C3 Substitution: Formation of Pyrrolo-Indoles and Cyclopentano-Indoles

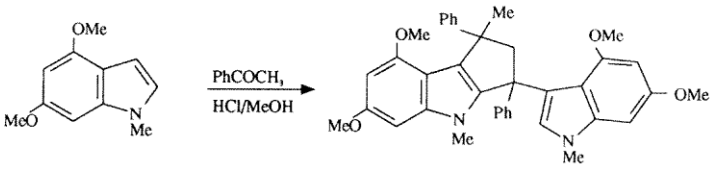
In an attempt to extend this reaction from aryl aldehydes to ketones, the indole (4) was reacted with several acetophenones. Conditions using phosphoryl chloride gave intractable mixtures but methanolic hydrogen chloride allowed the surprising formation in good yields of the pyrrolo[a]indoles (9) instead of di-indolylmethanes or macrocycles (Scheme 3). Again the same products could be formed from the related 2-substituted tertiary alcohols (10). The products (9) were obtained as a mixture of diastereomers, and the structure of the parent (Ar = Ph) confirmed by X-ray crystallography.



Scheme 3

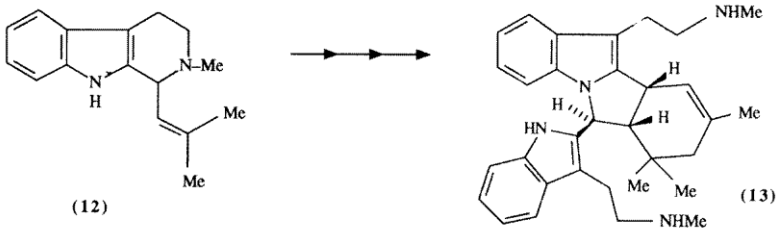
It is believed that dehydration of the tertiary alcohols (10) would yield 2-vinyl indoles (or related carbocations) capable of dimerization to give the products (9). One important aspect of this reaction is the absence of any attack at C7 and the methoxyl groups appear to play only a general activation role. For example, no reaction occurs between acetophenone and 3-methylindole, whilst 1-methylindole gives a 3,3'-diindolylmethane. 4,6-Dimethoxy-1-methylindole reacts with acetophenone in a manner analogous to the 3-methyl compound (4) to give a cyclopentano[b]indole (11), again as a mixture of diastereomers (Scheme 4).

Formation of compounds (9) and (11) is of interest in relation to the natural indoles isoborreverine (13) and yuehchukene (15) respectively. Isoborreverine is a minor constituent of *Borreria verticillata* and *Flindersia fournieri* and has been shown to arise by dimerization of borrerine (12) in a biomimetic synthesis (Tillequin *et al.*, 1978) (Scheme 5). The more important anti-fertility agent yuehchukene (15), from *Murraya paniculata* (Kong *et al.*, 1985) has been synthesised biomimetically from 3-isoprenylindole (14) (Cheng *et al.*, 1985; Wenkert *et al.*, 1988) (Scheme 5).

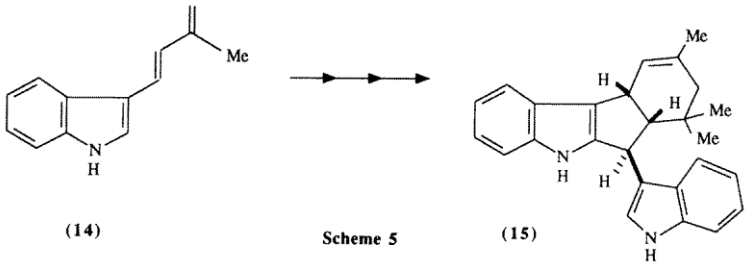


(11)

Scheme 4



(12) (13)

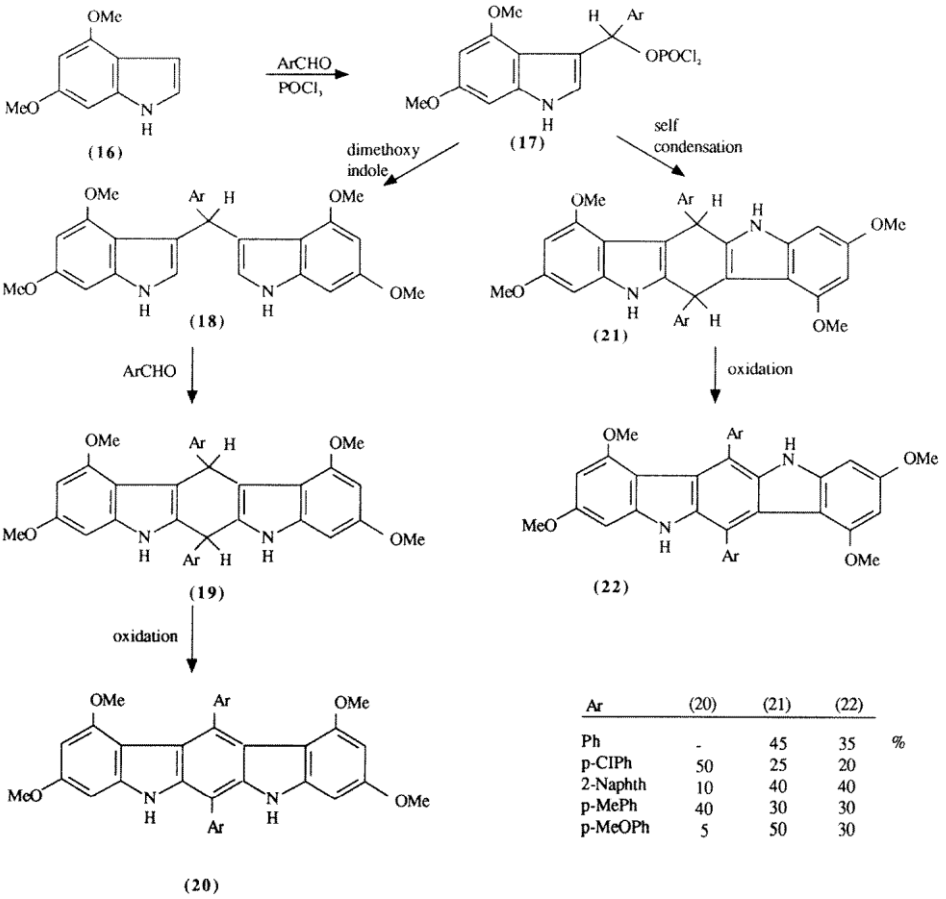


(14) Scheme 5 (15)

C2 and C3 Substitution: Formation of Carbazoles

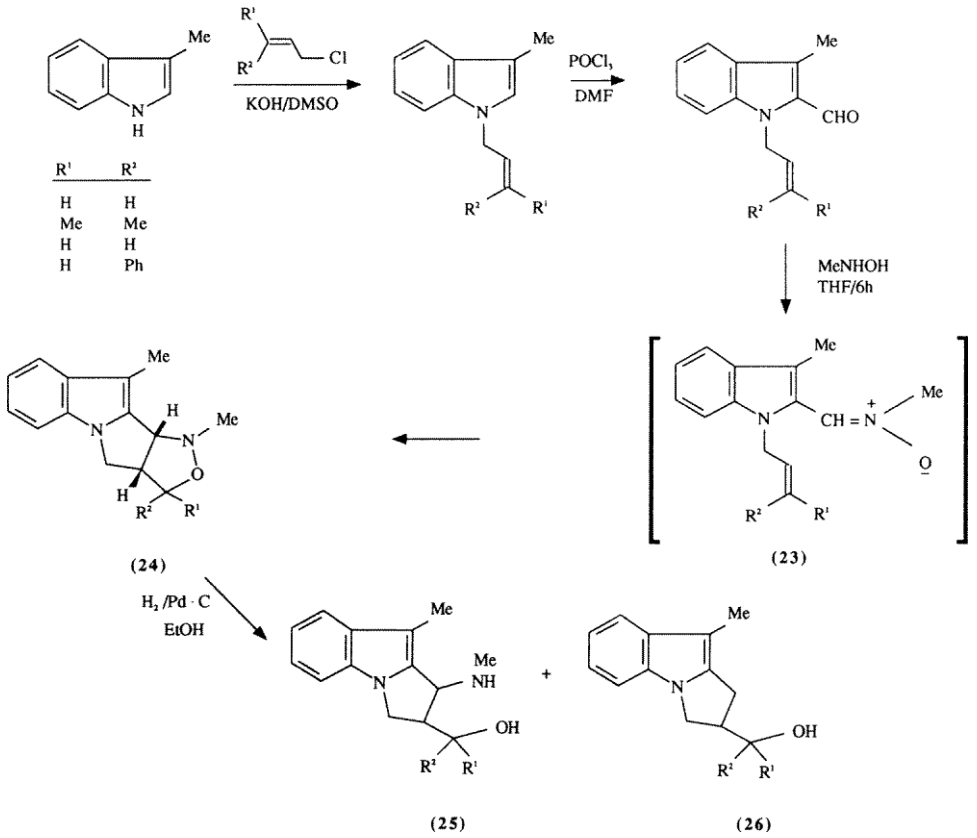
The reaction of the 3-methyl indole (4) with aryl aldehydes and phosphoryl chloride gave macrocyclic structures as the result of reaction at the two available sites, C2 and C7. 4,6-Dimethoxyindole (16) has three available reaction sites, C3, C2 and C7. It was found that reaction with aryl aldehydes and phosphoryl chloride gave indolo-carbazoles (20) and (22), together with the dihydro-analog (21) (Scheme 6). In this instance reaction has occurred at C3 and C2, but not at C7. Again indole itself does not undergo this reaction, so that the two methoxyl groups provide increased general reactivity, without selectively activating C7. Clearly the formation of a six-membered ring between C3 and C2, and its subsequent aromatization provide effective driving forces in this reaction.

The respective product yields are shown in Scheme 6. In all cases except for *p*-chlorobenzaldehyde there is a predominance of products arising from the self-condensation of the presumed intermediate (17) over those arising from the 3,3'-di-indolylmethane (18). It is noteworthy that none of the dihydro compound (19) could be detected, being presumably more readily oxidised to the indolocarbazole (20) than dihydro-compound (21) is oxidised to its related aromatic structure (22). The indolocarbazoles (20) and (22) offer new structures which are of interest because of the succession of five fused aromatic rings. They are reminiscent of some indole alkaloids (such as ellipticine) which show anti-tumour activity by their ability to intercalate into the DNA chain. There is clearly an opportunity to develop the chemistry of these new structural types.



Ar	(20)	(21)	(22)	
Ph	-	45	35	%
p-ClPh	50	25	20	
2-Naphth	10	40	40	
p-MePh	40	30	30	
p-MeOPh	5	50	30	

Scheme 6



Scheme 7

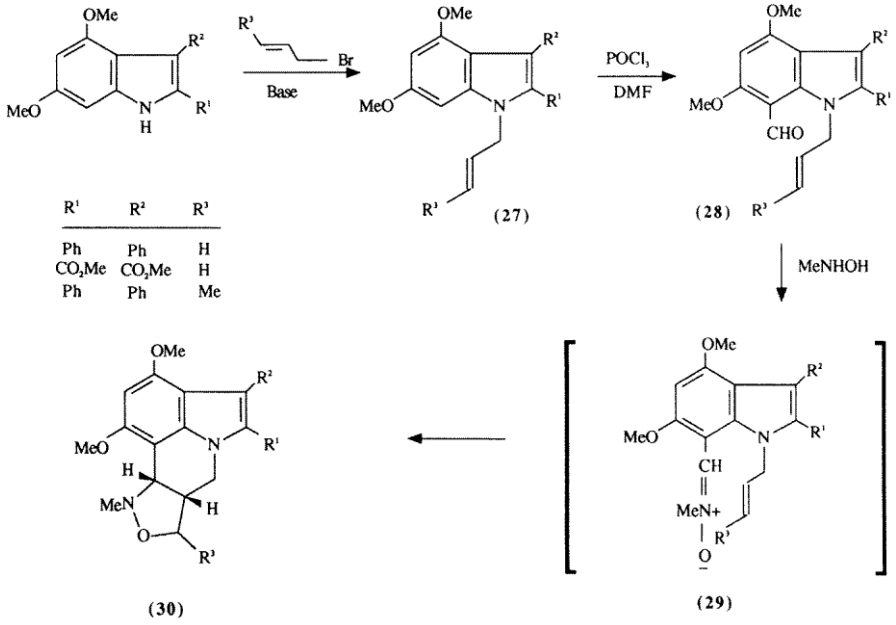
N1 and C2 Substitution: Formation of Pyrrolo-Indoles

The previously-described strategy of methoxyl group activation is not the only one able to build a five-membered ring between N1 and C2. A more direct approach simply involves a suitable intramolecular reaction between prearranged substituents at N1 and C2. We have chosen to investigate such an approach using intramolecular nitrone 1,3-dipolar cycloaddition. Thus a 3-methyl-*N*-allylindole can be formylated at C2, such that subsequent reaction with *N*-methylhydroxylamine affords the cycloadduct (24), presumably via an intermediate nitrone derivative (23) (Scheme 7).

The cycloadducts, (24) can be hydrogenolysed to give the amino-alcohols (25) as the major products, together with traces of some alcohols (26), which are the products of further reaction. Although we have not yet maximised yields, it is clear that either product could be obtained reasonably selectively, by an adjustment of reaction conditions.

N1 and C7 Substitution

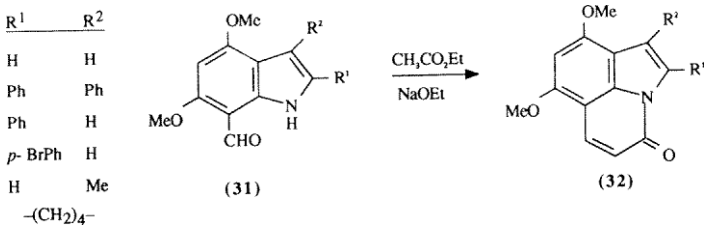
The intramolecular nitrone cycloaddition strategy can also be applied to cyclization between N1 and C7. Here, however, 4,6-dimethoxy activation is again required for substitution at C7. Thus formylation of the *N*-allyl indoles (27) gives the 7-formyl compounds (28) which undergo reaction with *N*-methylhydroxylamine to give the cycloadducts (30) in high yield, again presumably via a nitrone derivative (29) (Scheme 8).



Scheme 8

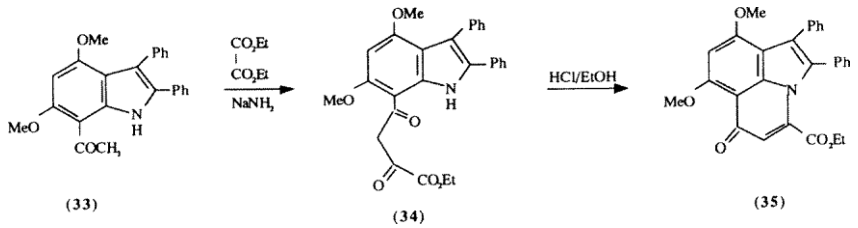
The cycloadducts (30) have yet to be submitted to further transformations.

Numerous possibilities arise for cyclization between substituents at N1 and C7 especially for the formation of pyrroloquinoline derivatives (Black and Kumar, 1990). For example, the 7-formyl compounds (31) can be reacted with ethyl acetate and sodium ethoxide to give excellent yields of the pyrrolo-quinolin-4-ones (32) (Black *et al*., 1989c) (Scheme 9).



Scheme 9

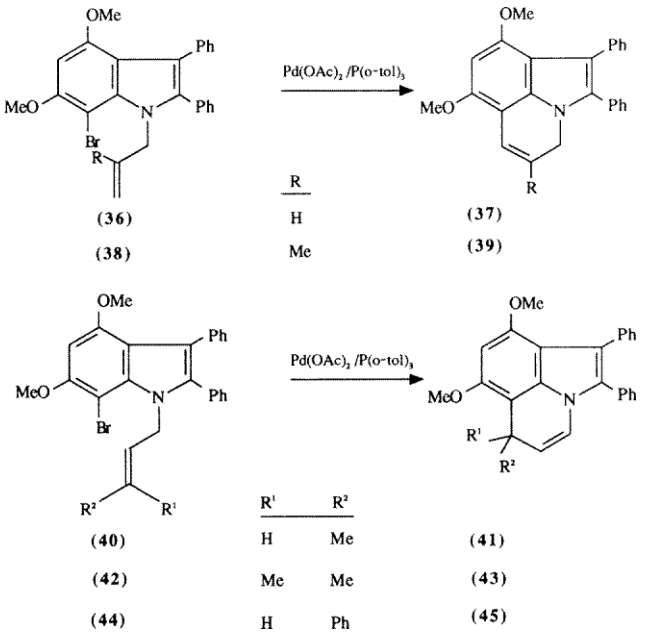
Alternatively, the pyrroloquinolin-6-one (35) can be prepared easily by acid-catalysed cyclization of the glyoxylic ester (34) derived in turn from the 7-acetyl indole (33) and diethyl oxalate in the presence of sodamide (Scheme 10).



Scheme 10

A more effective and general route for the formation of a six-membered ring between N1 and C7 involves the palladium-catalysed cyclization of a 7-bromo-*N*-allyl indole. The initial example involved the 7-bromo-*N*-allyl indole (36) which was generated by allylation of the related 7-bromoindole: bromination of the related *N*-allyl indole could not be achieved. On

treatment with palladium (II) acetate, tri-*o*-tolylphosphine and triethylamine in acetonitrile, indole (36) afforded a quantitative yield of the pyrroloquinoline derivative (37) (Scheme 11). This reaction was extended to the substituted allyl indoles (38), (40), (42), (44) which in turn yielded compounds (39), (41), (43), (45) respectively (Scheme 11). Double bond migration was observed to give both compounds (41) and (43). However, both products (39) and (45) were unstable and rapidly decomposed to tars, although spectroscopic evidence could be obtained for the proposed structures.

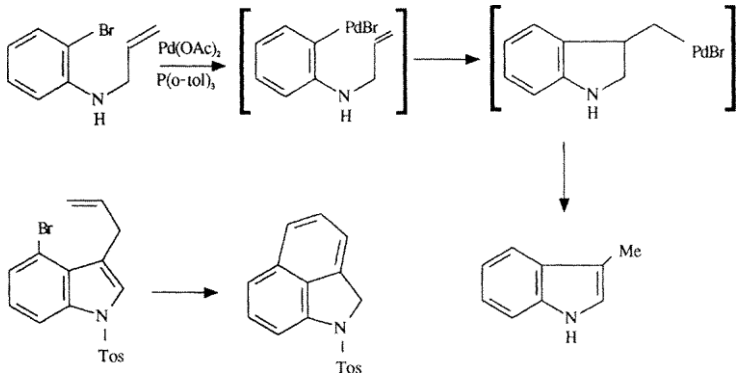


Scheme 11

It is significant that only six-membered ring formation occurred in these examples of peri-cyclization. This type of organopalladium cyclization was developed by Hegedus *et al*., (1978) as a 3-methyl indole synthesis from *o*-bromo-*N*-allylaniline via an arylpalladium intermediate (Scheme 12). More recently however, a similar reaction of the peri-substituted 3-allyl-4-bromoindole also gave selective six-membered ring formation (Harrington and Hegedus, 1984) (Scheme 12).

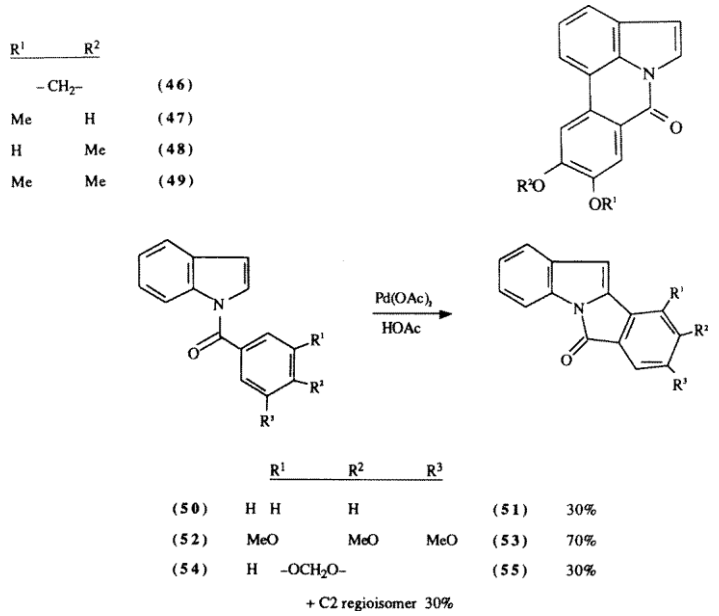
The success of this type of organometallic cyclization to give pyrroloquinolines led us to consider related methods for the synthesis of benzo-analogs such as the pyrrolophenanthridones, which form a small but interesting group of natural products from several Amaryllidaceae species. Examples are hippadine (46), pratorimine (47), pratorinine (48) and pratosinine (49).

Hippadine shows strong anti-fertility activity in rats and is under further biological investigation. Before our work commenced, hippadine had already been synthesised by two groups in very poor yields after very lengthy sequences (Hayakawa *et al*., 1987; Prabhakar *et al.*, 1987).



Scheme 12

Itahara (1979) had also shown that *N*-benzoylindole (50) underwent cyclization at C2, on treatment with a stoichiometric amount of palladium (II) acetate in acetic acid, to give product (51) in 30% yield. We then found that the oxygenated benzoyl indoles (52) and (54) gave higher yields of cyclized products (53) and (55) respectively, but still showed regioselectivity for C2 cyclization: no cyclization to C7 was observed (Scheme 13).

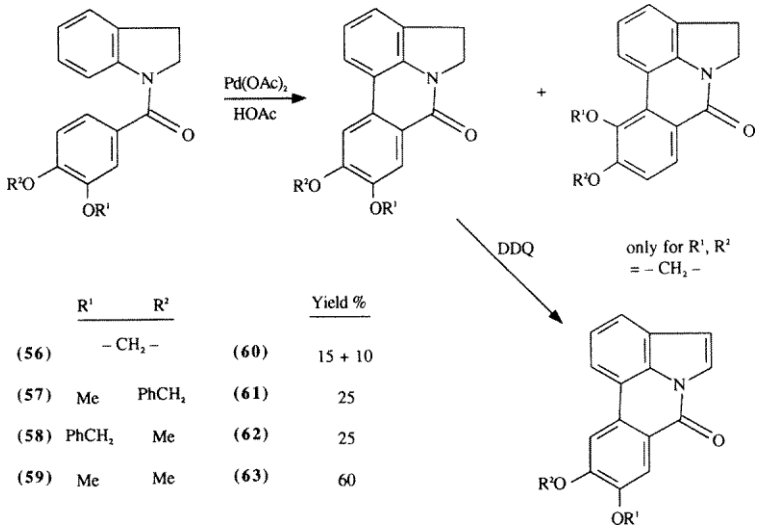


Scheme 13

Since cyclization of the *N*-aroylindoles occurred at C2, we removed this possibility by moving to the corresponding dihydroindoles. Indeed, palladium (II) acetate effected cyclization of the dihydroindoles (56 - 59) exclusively at C7, to give the phenanthridones (60 - 63), which could be oxidised by dichlorodicyanoquinone to the related indoles (Black *et al.*, 1989d). The choice of substituents was such that hydrogenolysis of benzyl groups afforded syntheses of pratorimine (47) and pratorinine (48) whilst hippadine (46) and pratosinine (49) were formed directly (Scheme 14).

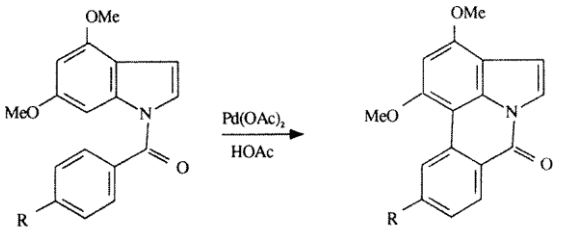
The dihydropyrrolophenanthridone (63) (formed in 60% yield) is also a known alkaloid, oxoassoanine (Llabres *et al.*, 1986). The hippadine precursor (56) was the only one to give a mixture of regioisomers. Although the yields are only modest and the key reaction has not yet been made catalytic, the route is very direct and certainly the most effective so far, despite a more recent synthesis involving intermolecular coupling (Siddiqui and Snieckus, 1990).

In view of our success with C7 activation by methoxyl substitution at C4 and C6, we investigated related cyclizations of *N*-aroyl-4,6-dimethoxyindoles (64). These were particularly successful, showing regioselectivity for C7 cyclization and also giving good yields (60-80%) of pyrrolophenanthridones (65) (Scheme 15).

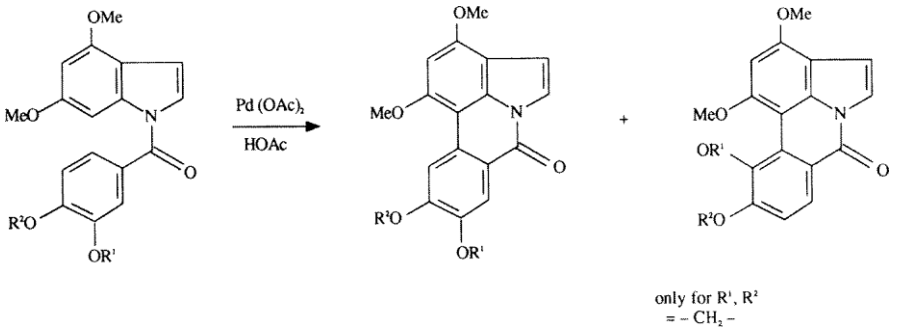


	R¹	R²		Yield %
	– CH_2 –			
(56)			(60)	15 + 10
(57)	Me	$PhCH_2$	(61)	25
(58)	$PhCH_2$	Me	(62)	25
(59)	Me	Me	(63)	60

Scheme 14



Scheme 15



R^1	R^2
$-CH_2-$	
Me	$PhCH_2$
$PhCH_2$	Me

Scheme 16

This approach was followed up in order to make the dimethoxy analogs of some of the pyrrolophenanthridone alkaloids. Here the yields were lower (30%) and again the methylenedioxy compound gave a mixture of regioisomers (Scheme 16).

It remains to be seen whether any of the dimethoxy compounds will emerge as natural products and it will also be of interest to see what effect the methoxyl groups have on the biological activity of these new analogues.

In summary, a wide range of new indole reactions has been discovered, by the use of 4,6-dimethoxy substitution. In some cases, this results in regioselective reaction at C7, our initial goal. However, the general increase in indole activity has led to the observation of quite new and exciting structures as a result of more conventional reaction at C3 and C2. Although our work has led to effective syntheses of some naturally-occurring indoles, it is more significant for the deliberate and accidental generation of totally unnatural products. We shall continue to investigate the chemistry of these new systems as well as the wider development of the reactivity of other highly activated indoles.

Acknowledgements

It is a pleasure to acknowledge the skill and dedication of Dr. Naresh Kumar, Mr Paul Keller, Dr. Renu Deb and Mr. Andrew Ivory, who performed the experimental work described. Financial support of the Australian Research Council is also greatly appreciated.

References

Black, D.St.C., Choy, A., Craig, D.C., Ivory, A.J. and Kumar, N., 1989a. Formation of 7,7'-bi-indolyls by oxidative dimerization of 4,6-dimethoxy-2,3-diphenylindole. *Journal of the Chemical Society, Chemical Communications,* 111-112.

Black, D.St.C., Craig, D.C. and Kumar, N., 1989b. Synthesis of a new class of indole-containing macrocycles. *Journal of the Chemical Society, Chemical Communications,* 425-426.

Black, D.St.C., Ivory, A.J., Keller, P.A. and Kumar, N., 1989c. A ready synthesis of 4-oxo-4H-pyrrolo[3,2,1-ij]quinolines. *Synthesis,* 322-323.

Black, D.St.C., Keller, P.A. and Kumar, N., 1989d. A direct synthesis of pyrrolophenanthridone alkaloids. *Tetrahedron Letters*, **30**, 5807-5808.

Black, D.St.C. and Kumar, N., 1984. A general strategy for the synthesis of 2,2'-, 2,3'-, and 2,7-bi-indolyls. *Journal of the Chemical Society, Chemical Communications,* 441-442.

Black, D.St.C. and Kumar, N., 1990. Pyrroloquinolines. *Organic Preparations and Procedures International,* in press.

Black, D.St.C., Kumar, N. and Wong, L.C.H., 1986a. Synthesis of 4,6-dimethoxyindoles. *Australian Journal of Chemistry,* **39**, 15-20.

Black, D.St.C., Kumar, N. and Wong, L.C.H., 1986b. Synthesis of 2-(7-indolyl)-benzimidazoles via 7-formylindoles. *Synthesis,* 474-476.

Black, D.St.C., Rothnie, N.E. and Wong, L.C.H., 1983. Metal template reactions. XX. Macrocyclic metal complexes derived from 4,6-dimethoxy-3-methylindole-2,7-dicarbaldehyde and some primary diamines with additional donor atoms. *Australian Journal of Chemistry*, **36**, 2407-2412.

Cheng, K.F., Kong, Y.C., and Chan, T.Y., 1985. Biomimetic synthesis of yuehchukene. *Journal of the Chemical Society, Chemical Communications,* 48-49.

Harrington, P.J. and Hegedus, L.S., 1984. Palladium-catalyzed reactions in the synthesis of 3- and 4-substituted indoles. Approaches to ergot alkaloids. *Journal of Organic Chemistry,* **49**, 2657-2662.

Hayakawa, K., Yasukouchi, T. and Kanematsu, K., 1987. A new approach to pyrrolophenanthridone alkaloids via allene intramolecular cycloaddition: total synthesis of hippadine. *Tetrahedron Letters,* **28,** 5895-5898.

Hegedus, L.S., Allen, G.F., Bozell, J.J. and Waterman, E.L., 1978. Palladium-assisted intramolecular amination of olefins. Synthesis of nitrogen heterocycles. *Journal of the American Chemical Society,* **100**, 5800-5807.

Itahara, T., 1979. Intrarnolecular ring closure of 1-aroylindoles by palladium acetate. *Synthesis,* 151-152.

Kong, Y.C., Cheng, K.F., Cambie, R.C. and Waterman, P.G., 1985. Yuehchukene : a novel indole alkaloid with anti-implantation activity. *Journal of the Chemical Society, Chemical Communications,* 47-48.

Llabres, J.M., Viladomat, F., Bastida, J., Codina, C. and Rubiralta, M., 1986. Phenanthridine alkaloids from *Narcissus assoanus. Phytochemistry,* **25**, 2637-2638.

Prabhakar, S., Lobo, A.M. and Marques, M.M., 1987. A new synthesis of the Arnaryllidaceae alkaloid hippadine. *Journal of Chemical Research* (S), 167.

Siddiqui, M.A. and Snieckus, V., 1990. Concise syntheses of the Amaryllidaceae alkaloids ungerimine and hippadine via the Suzuki aryl-aryl cross coupling reaction. *Tetrahedron Letters,* **31**, 1523-1524.

Tillequin, F., Koch, M., Pousset, J.L. and Cavé, A., 1978. Biomimetic synthesis of borreverine and isoborreverine. *Journal of the Chemical Society, Chemical Communications,* 826-828.

Wenkert, E., Moeller, P.D.R., Piettre, S.R. and McPhail, A.T., 1988. Yuehchukene analogues. *Journal of Organic Chemistry,* **53**, 3170-3178.