INDOLOQUINAZOLINES: A CENTURY IN REVIEW

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Abstract - The synthesis and reactions of the four known isomeric tetracyclic indoloquinazolines.

Dedicated to the memory of Dr. Yoshio Ban.

CONTENTS

I. INTRODUCTION

Indoloquinazolines have been known since 1892 when O'Neill[1] synthesized 6,12-dihydro-6,12-dioxoindolo[2,1-*a*]quinazoline (**7**) for the first time. Indoloquinazolines have a central tetracyclic system formed by the fusion of two heterocycles - indole (**1**) and quinazoline (**2**), and hence the name indoloquinazoline. The four known indoloquinazolines are indolo[1,2-*a*]quinazoline (**3**), indolo[1,2-*b*]quinazoline (**4**), indolo[1,2-*c*]quinazoline (**5**) and indolo[4,3-*fg*]quinazoline (**6**).

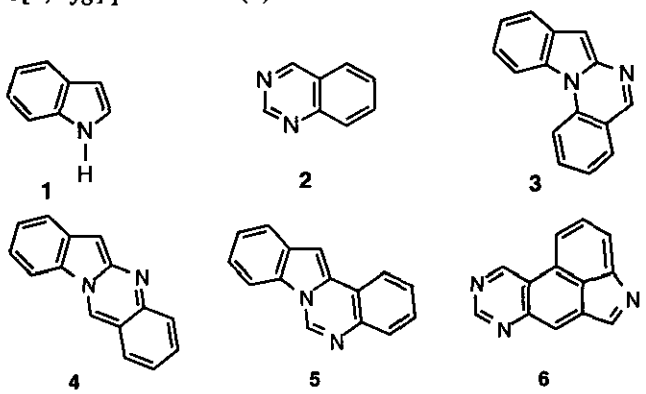
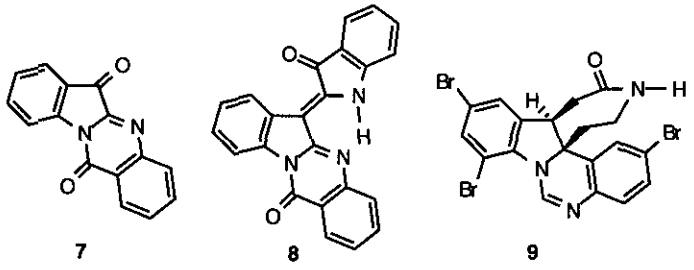


Figure 1

Though numerous alkaloids containing either an indole unit or a quinazoline unit are known, only three alkaloids are known which belong to the indoloquinazoline family. Tryptanthrin (**7**), also known as couropitine A or anhydroisatin-α-anthranilide, and candidine (**8**), also known as qingdainone, contain the indolo [2,1-*b*]quinazoline (**4**) nucleus, whereas hinckdentine A (**9**) contains the indolo[1,2-*c*]quinazoine (**5**) nucleus.



7 **8** **9**

Figure 2

No alkaloid derived from indolo[1,2-*a*]quinazoline (**3**) or indolo[4,3-*fg*]quinazoline (**6**) is known.

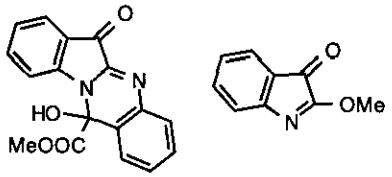
Tryptanthrin (**7**) and candidine (**8**) exhibit potent biological activity, but that of hinckdentine A has not been studied yet. The importance of the indolo[4,3-*fg*]quinazoline (**6**) ring system lies in the fact that it resembles the nucleus of the ergotine alkaloids, which exhibit wide range of bioactivity.

Tryptanthrin (**7**) has been found to have antimycotic activity against dermatophytes and has specific activity against those causing athlete's foot. Tryptanthrin (**7**) and candidine (**8**) have also been found to be active in tests against melanoma B_{16}. Candidine (**8**) has also shown inhibitory action against Lewis lung carcinoma in mice.

The resultant pharmacological interest in **7** and **8** has led to the development of numerous synthetic routes for their synthesis, which in turn has led to the study of the basic chemistry of **4** to some extent. However, the chemistry of **3**, **5** and **6** has been only sparsely investigated. In this article we have reviewed the isomeric indoloquinazolines - their chemistry, syntheses, and applications, from 1892 to 1994.

II. Indolo[2,1-*b*]quinazolines

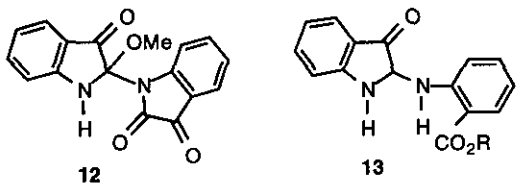
Tryptanthrin (**7**)[2] and candidine (**8**) are the best known derivatives of **4**. Though tryptanthrin (**7**) was the first derivative of **4** to be synthesized, the alkylisatoids and specifically methylisatoid (**10**) garnered the attention of chemists in the early twentieth century. Controversy raged between the two German chemists Hantzsch[3,4] and Heller[5-8] regarding the structure of methylisatoid, a compound which was first obtained by the exposure of *O*-methylisatin (**11**) to moist air.



10 **11**

Figure 3

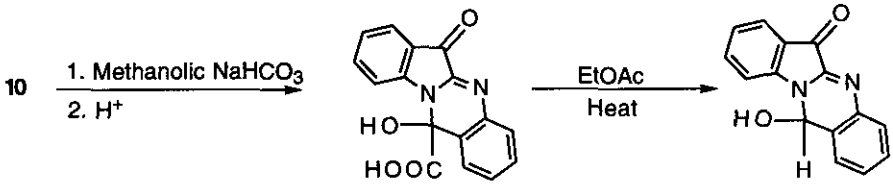
While Hantzsch suggested **12** as the structure of methylisatoid, Heller suggested structure (**13**).



12 13

Figure 4

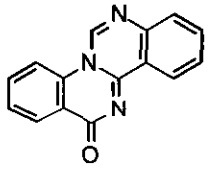
Controversy flared again when Bird[9] in 1963 supported the Hantzsch structure. Cornforth[10] finally showed that **10** was a methyl ester by hydrolyzing it to the corresponding acid (**14**), which was then decarboxylated to give the alcohol (**15**).



14 15

Scheme 1

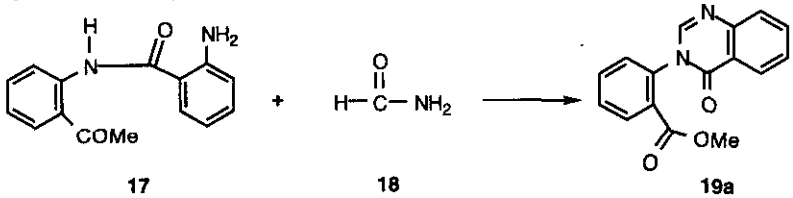
Butler and coworkers[11] attempted to synthesize triazachrysenone (**16**), a tetracyclic dipyrimidinone.



16

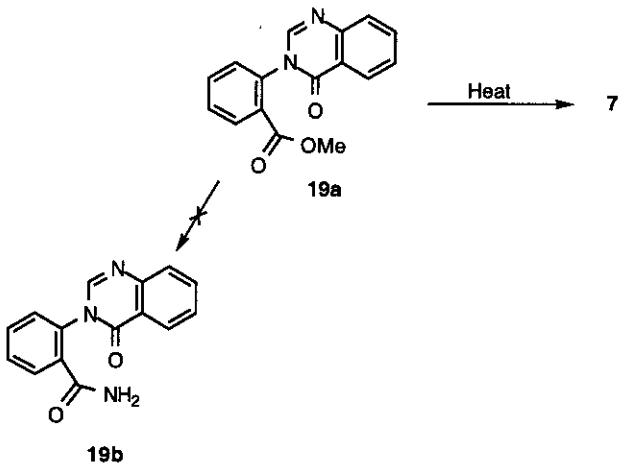
Figure 5

They synthesized the ester (**19a**) by the reaction of methyl-2,2'-aminobenzamidobenzoate (**17**) with formamide (**18**). However, they could not convert **19a** to the corresponding amide (**19b**), a precursor of **16**. However, the ester (**19a**) undergoes thermal cyclization to form **7**.



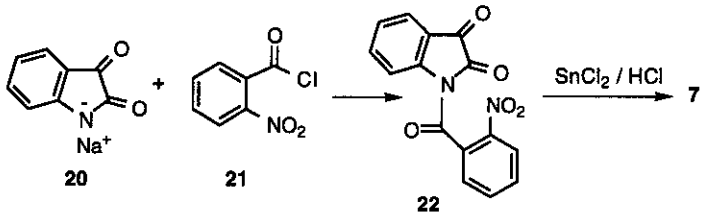
17 18 19a

(scheme continued)



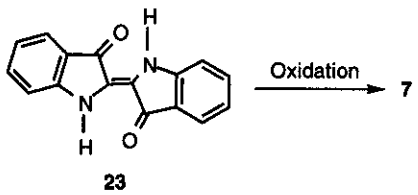
Scheme 2

Kikumoto and coworkers[12] found that the reaction of *N*-sodioisatin (**20**) with *o*-nitrobenzoyl chloride (**21**) resulted in the formation of 1-(2'-nitrobenzoyl)isatin (**22**) which on reduction gave **7**.



Scheme 3

The oxidation of indigo (**23**)[13] also results in the formation of **7**.



Scheme 4

Bond and coworkers[14] attempted to synthesize isatogens (**24**) using acetylides.

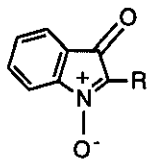
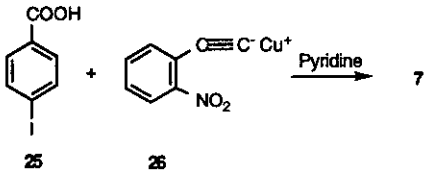


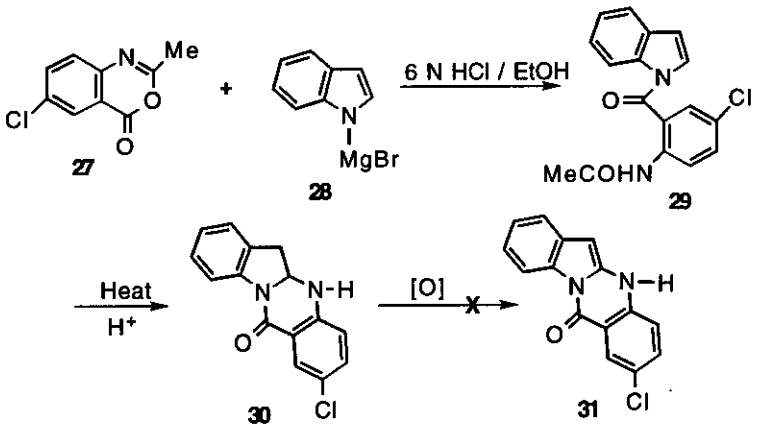
Figure 6

They found that the treatment of 4-iodobenzoic acid (**25**) with acetylide (**26**) in pyridine results in the formation of **7** in low yields. The same result was obtained when 2-bromopyridine was reacted with **24**.



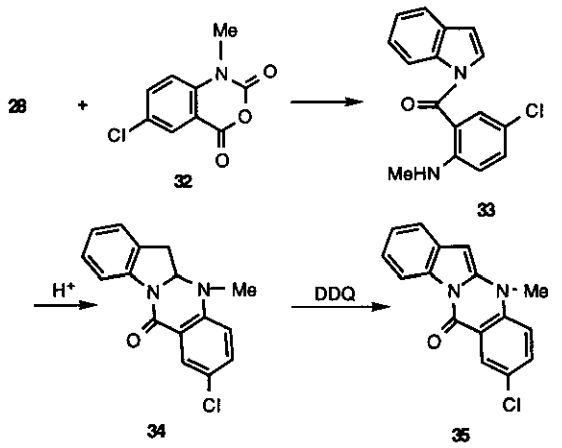
Scheme 5

The reaction of **27** with the indole Grignard (**28**)[15] results in the formation of 1-substituted indole (**29**), which undergoes cyclization under acidic conditions to give the indolo[2,1-*b*]quinazoline derivative (**30**).



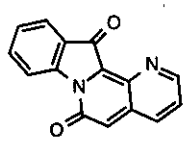
Scheme 6

Though sensitive to a variety of reagents, **30** could not be oxidized to **31**. Alternately, the product (**33**) obtained by the reaction of **28** with 5-chloro-*N*-methylisatoic anhydride (**32**), on treatment with acid cyclizes to give **34** which is readily oxidized by DDQ to give **35**.



Scheme 7

In 1974, Dutta and coworkers[16] isolated a yellow compound from the fruits of the cannonball tree *Couroupita guianensis* and called it couropitine A; they assigned the erroneous structure (**36**) to it.



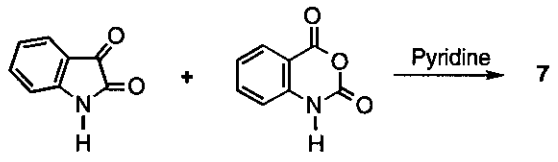
36

Figure 7

In 1971, Zahner and coworkers[17] had isolated a yellow compound from cultures of the yeast *Candida lipolytica* by feeding it large amounts of tryptophan and anthranilic acid, and called it tryptanthrin (**7**). It was found that by feeding the yeast with suitably substituted tryptophans and anthranilic acid, different derivatives of **7** could be isolated. Fedeli and coworkers[18] determined the structure of tryptanthrin by X-ray crystallography and found it to be **7**. Later, it was shown that couropitine A and tryptanthrin are the same compound and the name tryptanthrin was retained.[19] Tryptanthrin (**7**) was also isolated from the cultures of the fungus *Leucopaxillus cerealis*.[20] Japanese workers[21-23] later isolated **7** from *Polygonum tinctorium* and *Isatis tinctoria*. The leaves of *Strobilanthes cusia* are used in Okinawa for treatment against dermatophytic infections, specifically athlete's foot. Honda and co-workers[21-23] found that tryptanthrin (**7**) was the active ingredient in these leaves.

The antibiotic property[21] of tryptanthrin (**7**) resulted in a flurry of activity concerning its synthesis and that of its analogs.

The treatment of isatin (**37**) with hot potassium permanganate results in the formation of **7** in very low yields.[13] Tryptanthrin (**7**) can be synthesized in good yield by treating isatin with isatoic anhydride (**38**) in pyridine.[19]

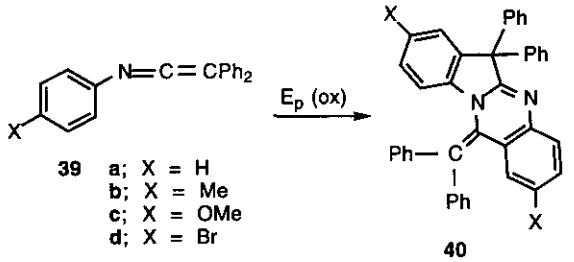


37 **38**

Scheme 8

The use of methylpiperidine as catalyst improves the yield. Further improvements involve using diisopropyl carbodiimide or excess isatoic anhydride as a trap for water.[24] As a result, 2-chlorotryptanthrin can be synthesized from 6-chloroisatoic anhydride and isatin whereas 8-chlorotryptanthrin can be synthesized from 5-chloroisatin and isatoic anhydride.[20] Karpf and Junek[25] showed that isatin can also be self-condensed to **7** using a carbon dioxide laser.

In recent times, heterocumulenes have been used in the synthesis of heterocycles. Becker and coworkers[26] have shown that the preparative electrochemical oxidation of ketene imines of the type (**39**) results in the formation of the tryptanthrin related compounds (**40**) in good yields.

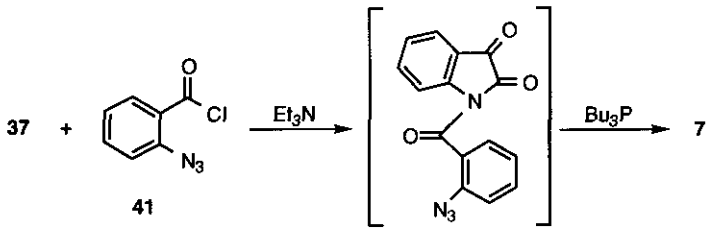


39 **a**; X = H
b; X = Me
c; X = OMe
d; X = Br

40

Scheme 9

A mechanism for the formation of dimers of the type (**40**) has been proposed by Becker and coworkers.[27]
The intramolecular aza-Wittig reaction has been employed by Eguchi and coworkers[28] in synthesizing derivatives of **7**. Thus, the reaction of isatin (**37**) with *o*-azidobenzoyl chloride (**41**) followed by the treatment of the intermediate (**42**) with tributylphosphine, resulted in the formation of **7**.

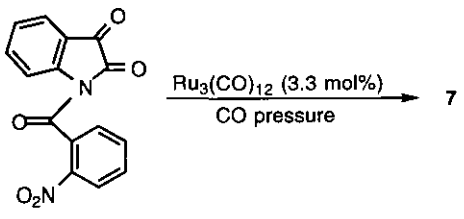


41

42

Scheme 10

An improvement in yield was observed when 10 mol % of 4-diethylaminopyridine was added.
Recent advances in transition metal chemistry have shown that transition metal complexes can be used for the synthesis of heterocyclic ring systems.[29] Thus, reductive cyclization of *N*-(2-nitrobenzoyl)isatin (**43**) using ruthenium carbonyl led to the formation of **7** in moderate yields.



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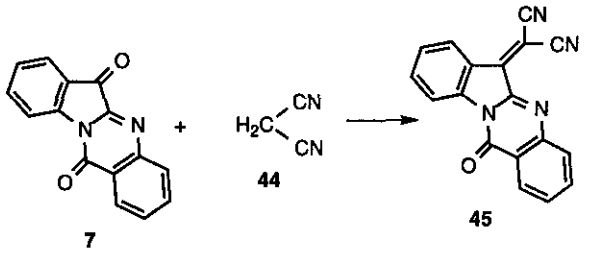
Scheme 11

The chemistry of tryptanthrin (**7**) has been found to be similar to that of isatin (**37**).[30-33] The solubility of **7** in water and simple alcohols is very limited. The reaction of tryptanthrin (**7**) with amines results in the formation of

intense blue dyes. The ability of **7** to dehydrogenate α-amino acids and subsequently convert them to secondary products may be an indication of its mechanism of antimicrobial action on dermatophytes.[21]

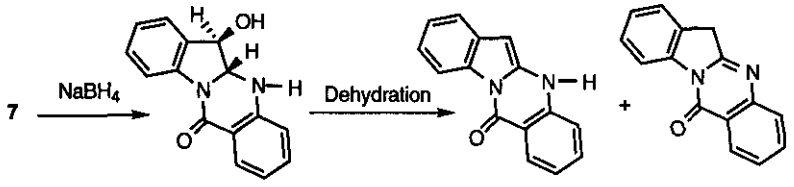
The 6-oxo group of **7** undergoes condensation reactions with compounds bearing active methylene groups. Thus, the reaction of **7** with nitrile (**44**) led to the formation of condensation product (**45**).[34]



7 **44** **45**

Scheme 12

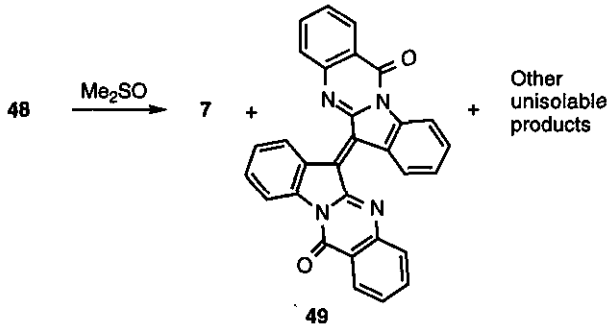
The sodium borohydride reduction of **7** resulted in the formation of the alcohol (**46**) which was then dehydrated with sulfuric acid or polyphosphoric acid to the corresponding tautomers (**47**) and (**48**).[34]



46 **47** **48**

Scheme 13

Mild oxidation of **48** led to the formation of **7** and the dimeric product (**49**), though in acidic medium (BF_3 - HOAc) only **49** was formed.[34]



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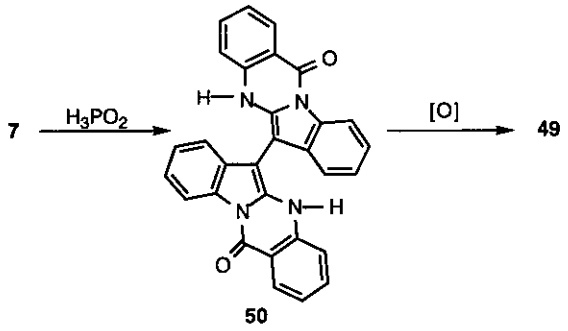
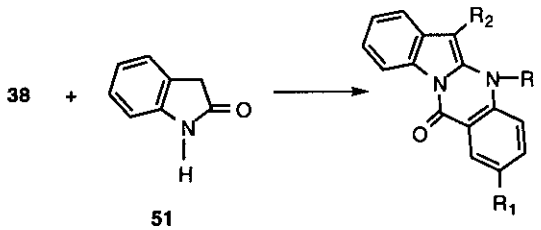
Scheme 14

Treatment of **7** with hypophosphorous acid (H_3PO_2) afforded the coupling product (**50**) which was readily oxidized to give **49**.



Scheme 15

By using a suitably *N*-substituted isatoic anhydride (**38**) and oxindole (**51**), a series of derivatives (**52a-e**) were synthesized.[34]



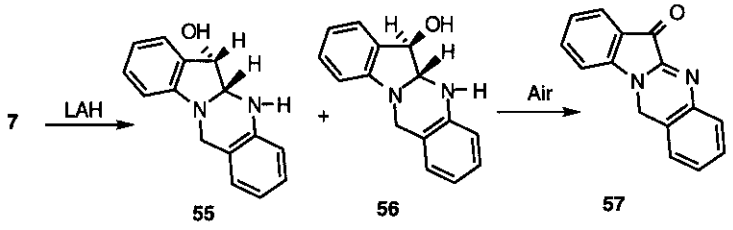
52 **a** ; R = H; R_1 = H; R_2 = H
b ; R = Me; R_1 = H; R_2 = H
c ; R = COMe; R_1 = H; R_2 = H
d ; R = Me; R_1 = Cl; R_2 = H
e ; R = H; R_1 = H; R_2 = Me

Scheme 16

These derivatives could also be synthesized by the oxidation of appropriate precursors. Thus **52b** was prepared by the manganese dioxide oxidation of **53**.[34] Alternately, **52b** was also prepared by desulfurization of **54** using Raney nickel.[34]

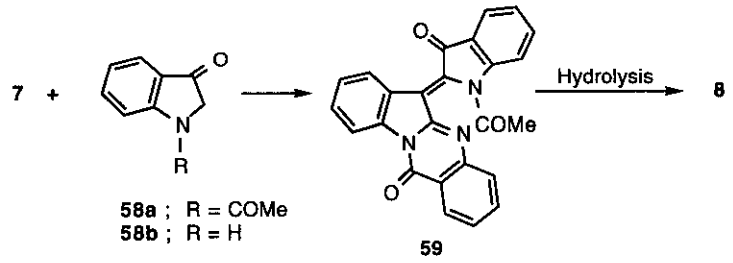
Scheme 17

The lithium aluminum hydride reduction of **7** led to the formation of 6-*cis* (**55**) and 6-*trans* (**56**) alcohols which could then be dehydrogenated to give **57**.[34]



Scheme 18

Along with tryptanthrin (**7**), Zahner and Fiedler[17,36] had isolated an unidentified violet colored compound from the culture of the yeast *Candida lipolytica* and named it candidine (**8**). The structure of candidine (**8**) was determined by Bergman and Tilstam[35] in 1985. It was found to be the condensation product of tryptanthrin (**7**) and indoxyl (**58b**). It was synthesized by them by condensing tryptanthrin (**7**) with *N*-acetylindoxyl (**58a**) followed by mild hydrolysis.



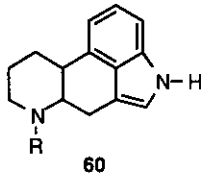
Scheme 19

Actually, in 1922 Martinet and Grosjean[37] had already briefly described candidine as a condensation product of tryptanthrin (**7**) and indoxyl (**58b**). The leaves of the plants *Baphicacanthus cusia* and *Isatis tinctoria* were used by the Chinese to prepare a traditional medicine Qing Dai. Zou and coworkers[38] isolated the active constituent and named it quingdainone, but it was later identified as candidine.[39] Candidine (**8**) was also obtained in small amounts by the enzymatic cleavage of blood plasma, urine and haemofiltrate of uraemic patients.[40] Candidine (**8**) has been found to have antimicrobial activity and is also active against melanoma B_{16}.[38] It has also been found to be active against Lewis lung carcinoma in mice.[38]

The best method of synthesizing candidine is still by condensing **7** with indoxyl (**58b**).

III. Indolo[4,3-*fg*]quinazolines

The interest in indolo[4,3-*fg*]quinazoline (**6**) and its derivatives is quite recent. The interest in **6** has been sparked because of the similarity of the ring system of **6** with that of the ergoline ring system (**60**).[41]

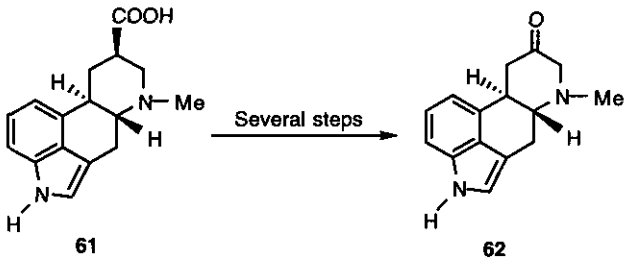


60

Figure 8

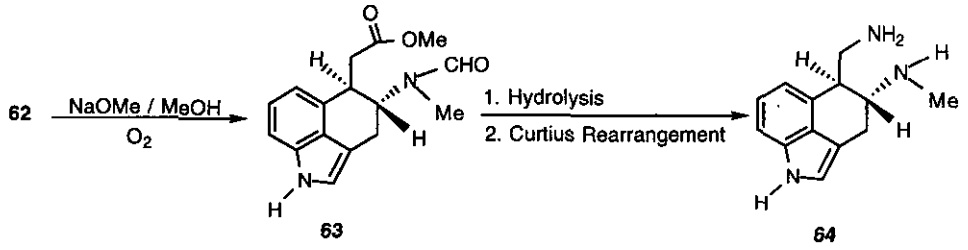
Ergoline derivatives have generated substantial interest from the pharmaceutical viewpoint[42,43] because of their ability to control prolactin release, as drugs in the treatment of Parkinson disease and also as central vasodilators. It has been shown that the entire ergoline skeleton is not essential for bioactivity[44,45] and consequently derivatives of **6** could also be of pharmacological interest.

Mantegani and coworkers[41] devised a semisynthetic route towards the derivatives of **6** starting from dihydrolysergic acid (**61**), which was converted to 6-methyl-8-oxoergoline (**62**) in several steps. Starting the synthesis with **61** was advantageous in the fact that the stereochemistry was fixed right from the beginning.



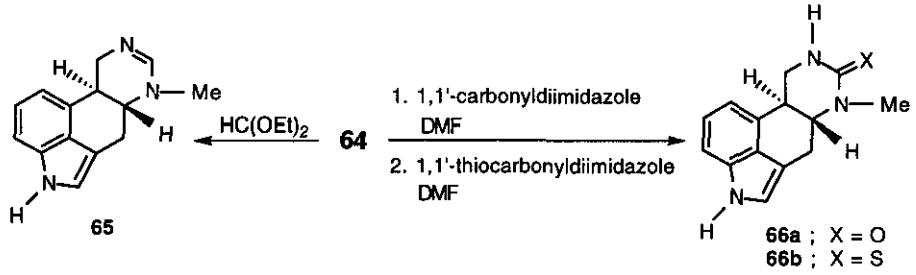
Scheme 20

The piperidone ring of **62** was cleaved to give the amido ester (**63**) as a major product which was then hydrolysed to the corresponding acid. Curtius reaction on the acid led to the formation of diamine (**64**), a precursor of the derivatives of **6**.



Scheme 21

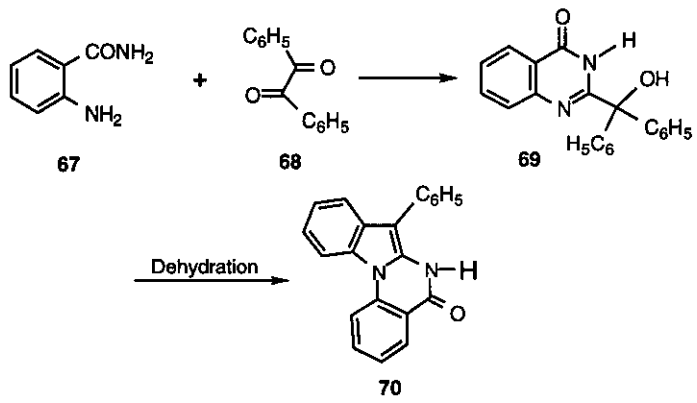
The reaction of **64** with suitable reactants gave varied derivatives of **6**.



Scheme 22

IV. Indolo[1,2-*a*]quinazoline

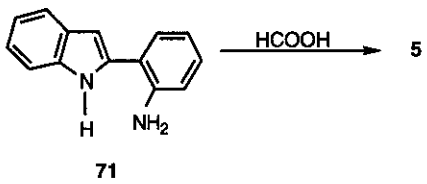
Of the four known indoloquinazolines, **3** is the least known, since only one derivative of it has been reported. Moore and coworkers[46] were trying to prepare compounds analogous to tropone containing a seven membered unsaturated ring. They reacted anthranilamide (**67**) with benzil (**68**) and the product (**69**) obtained was dehydrated to give a yellow, weakly acidic compound which was assigned structure (**70**).



Scheme 23

V. Indolo[1,2-*c*]quinazoline

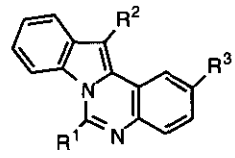
Indolo[1,2-*c*]quinazoline (**5**) was first synthesized by Kiang and coworkers[47] in 1956 by heating 2-(2'-amino)phenylindole (**71**) with formic acid.

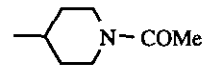
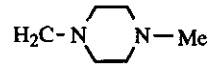


Scheme 24

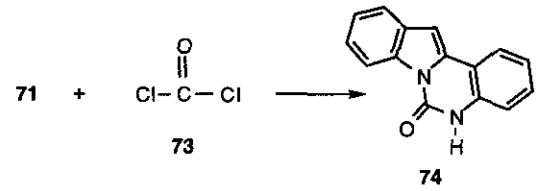
Its derivatives, 6-methyl- (**72a**) and 6-benzylindolo[1,2-*c*]quinazoline (**72b**) were synthesized by reacting 2-(2'-amino)phenylindole (**71**) with acetyl and benzoyl chlorides respectively. Robinson and coworkers[48] were able to synthesize 6,12-dimethyl derivative (**72c**) by a Fischer indole cyclization and subsequent acid treatment, starting from the hydrazone of 2-aminophenyl ethyl ketone and phenylhydrazine.

Table 1. Derivatives (72a-k) of indolo[1,2-*c*]quinazoline (5).



72	R^1	R^2	R^3
a	Me	H	H
b	$C_6H_5CH_2$	H	H
c	Me	Me	H
d	CH_2Cl	H	H
e	CH_2Cl	H	Cl
f	$CH_2C_6H_4Cl$	H	H
g	CH_2CH_2COOH	H	H
h	$CH_2CH_2CON(Et)_2$	H	H
i		H	H
j		H	H
k	Me	Ph	H

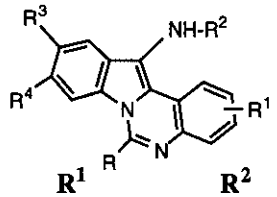
Duncan and coworkers[49] synthesized compounds (**72d-j**) by reacting a suitably substituted 2-(2'-amino)phenylindole with the appropriate acyl chloride. Gatta and coworkers[50] were able to synthesize **72k**. Bergman and coworkers[51] reacted 2-(2'-amino)phenylindole (**71**) with phosgene (**73**) to obtain the 6-oxo derivative (**74**).



Scheme 25

A group of Russian workers[52-55] employed an *o*-benzidine type rearrangement in the indole series as the key step in the synthesis of a number of derivatives (**75a-v**) of indolo[1,2-*c*]quinazoline.

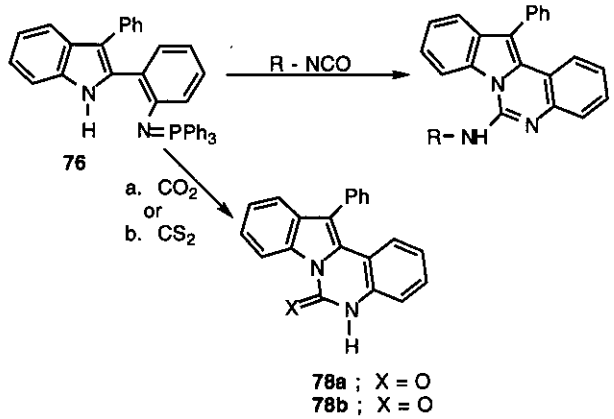
Table 2. Derivatives (75a-v) of indolo[1,2-*c*]quinazoline (5).



75	R	R^1	R^2	R^3	R^4
a	Me	H	COMe	H	H
b	Me	H	H	H	H
c	Me	o-Me	COMe	H	H
d	Me	p-Me	H	H	H
e	Me	p-Cl	COMe	H	H
f	Me	p-Cl	H	H	H
g	$PhCH_2$	H	COMe	H	H
h	Me	P-CO_2Et	COMe	H	H
i	Ph	H	COMe	H	H
j	Ph	H	H	H	H
k	Me	NO_2	H	H	H
l	Me	NO_2	COMe	H	H
m	Me	H	H	H	H
n	Me	H	COMe	Br	H
o	Me	Cl	H	Br	H
p	Me	Cl	COMe	Br	H
q	Me	H	H	Br	NO_2
r	Me	H	COMe	H	NO_2
s	Me	Cl	H	H	NO_2
t	Me	Cl	COMe	H	NO_2
u	Me	NMO_2	H	H	NO_2
v	Me	NO_2	COMe	H	NO_2

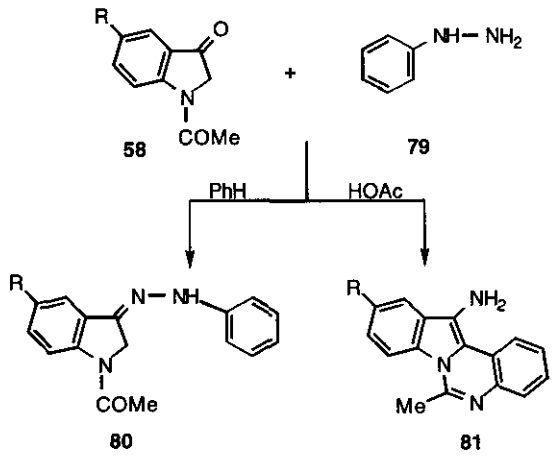
They also found that the 5,6-double bond of **5** could be readily reduced by sodium borohydride.[56]

The synthesis of indolo[1,2-*c*]quinazoline derivatives can also be achieved by an aza-Wittig type reaction of an iminophosphorane intermediate (**76**)[57] with an aromatic isocyanate as well as with carbon dioxide or carbon disulfide to give **77** and **78**, respectively.



Scheme 26

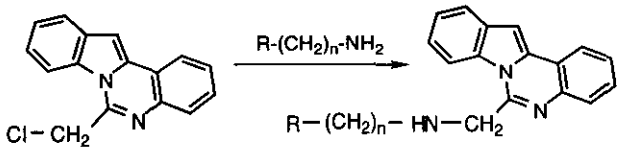
Heating substituted oxoindoles (**58**) with phenylhydrazine (**79**) gave the corresponding hydrazones (**80**). However, under acidic conditions an *o*-benzidine rearrangement of hydrazones (**80**) takes place followed by cyclization, giving substituted indolo[1,2-*c*]quinazolines (**81**).[56]



Scheme 27

Many derivatives of indolo[1,2-*c*]quinazoline (**5**) have been claimed to be cataleptogenic agents[55] and have been extensively patented.

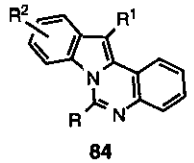
Duncan[59] has patented compounds of the type (**83**) which were prepared by reacting **82** with an appropriate amine.



83 **a** ; n = 1, R = morpholino
b ; n = 1, R = pyrrolidino
c ; n = 0, R = 1-acetyl-4-piperidyl

Scheme 28

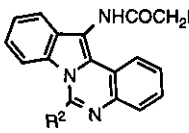
Russian workers[60-63] have patented a number of compounds of the type (**84**) and (**85**), synthesized *via* an *o*-benzidine rearrangement of the appropriate hydrazones.



84

R = H or alkyl
R^1 = H, alkyl, arylazo, amino, acylamino
R^2 = H, halo, alkyl, alkoxy

(figure continued)

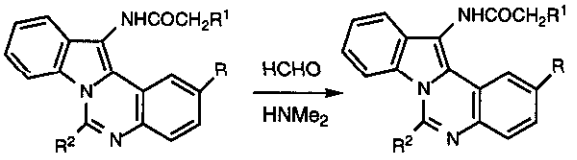


R = H, Me, Cl
R^1 = NMe_2, NEt_2, piperidino, morpholino, methylpiperazino, adamantylamino
R^2 = Me

85

Figure 9

Mannich reactions of compounds of the type (**86**) resulted in the formation of Mannich bases (**87**) in moderate yields.



86 a ; R = H, Me
R^1 = morpholino
R^2 = Me

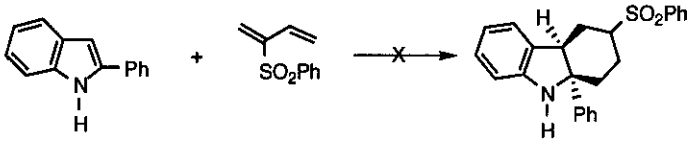
b ; R = R_2 = Me
R^1 = NEt_2, piperidine

87 a ; R = H, Me
R^1 = morpholino
R^2 = $Me_2NCH_2CH_2$

b ; R = H
R^1 = NEt_2, piperidin
R^2 = $Me_2NCH_2CH_2$

Scheme 29

Hinckdentine A (**9**), the only natural product based on the indolo[1,2-*c*]quinazoline ring system, was isolated by Blackman and coworkers[64] in 1987 from the Tasmanian bryozoan *Hincksinoflustra denticulata*. The structure of **9** was established by X-ray crystallography and its stereochemistry was established by detailed nmr studies.
Although no bio-testing of **9** has been carried out, many derivatives of indolo[1,2-*c*]quinazoline have found some kind of biological application, making hinckdentine A a potentially useful compound.
The first reported study aimed at synthesizing **9** foundered when attempts to synthesize model starting compound (**90**) by reacting the Grignard, the lithio or the potassio derivative of 2-phenylindole (**88**) with 2-phenylsulfonyl-1,3-butadiene (**89**) failed[65].

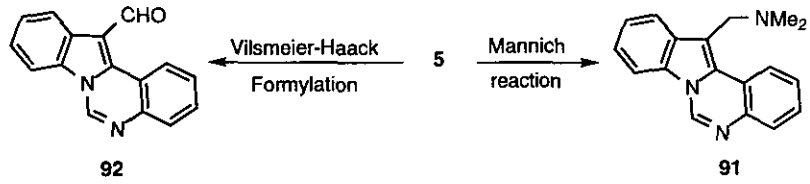


88 (as anion) **89** **90**

Scheme 30

In a recent publication[66] by the authors, a systematic study of the reactions of indolo[1,2-*c*]quinazoline (**5**) was made, as well as attempts to employ **5** as a synthon for the construction of the pentacyclic skeleton of hinckdentine A (**9**).

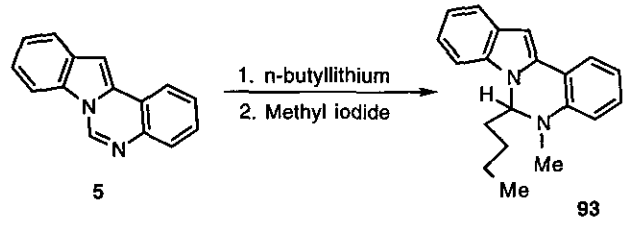
Position 12 of **5** corresponds to position 3 of indole. Consequently, the Mannich reaction and the Vilsmeier-Haack formylation of **5** gave the gramine (**91**) analog and the formyl dervative (**92**), respectively.



92 91

Scheme 31

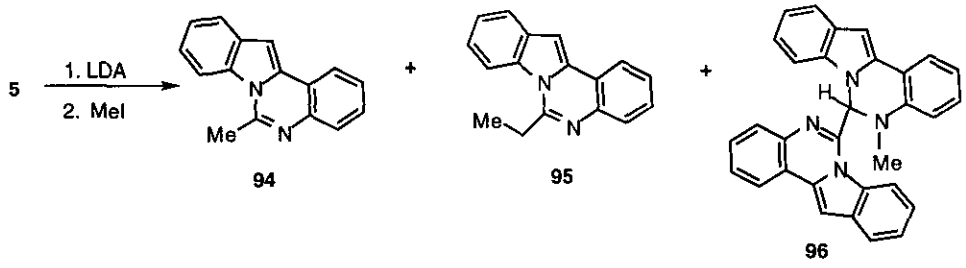
The metallation reaction of **5** with n-butyllithium resulted in the formation of an addition product, isolated as the *N*-methyl derivative (**93**).



5 93

Scheme 32

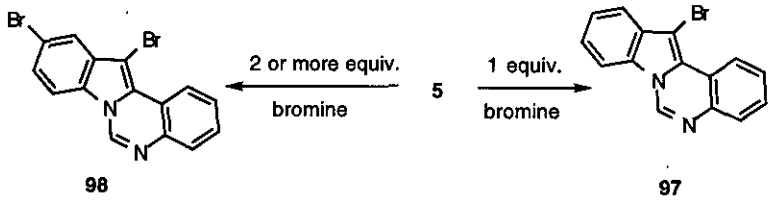
The use of 1.25 equivalents of the non-nucleophilic base lithium diisopropylamide (LDA), followed by methylation, resulted in the formation of the 6-methyl derivative (**94**) as the major product, with smaller amounts of the 6-ethyl derivative (**95**) and the dimeric product (**96**).



94 95 96

Scheme 33

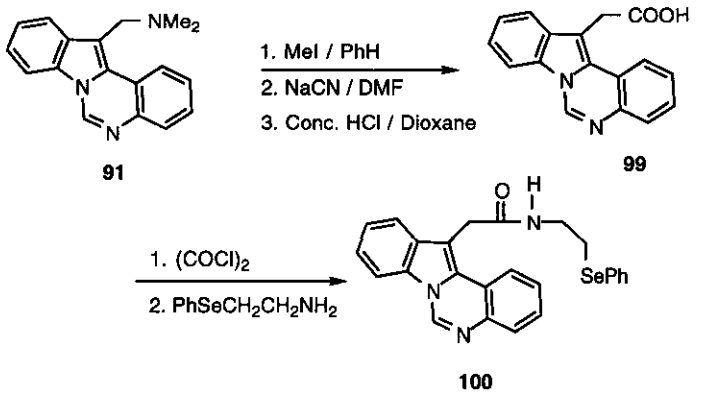
The natural product hinckdentine A has three bromine substituents. The direct bromination of **5** using one equivalent of bromine gave the 12-bromo compound (**97**) as major product with smaller amounts of the 10, 12-dibromo compound (**98**). The use of two or more equivalents of bromine resulted only in the formation of **98** as the major product, implying that the three bromines in the natural product (**9**) are not introduced biogenetically from a fully aromatic indolo[1,2-*c*]quinazoline precursor.



Scheme 34

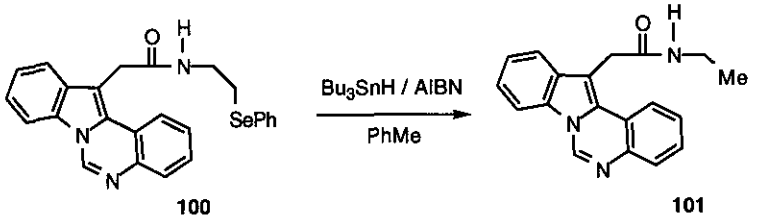
The strategy conceived for synthesizing the skeleton of hinckdentine A (**9**) involved fuctionalizing the position 12 of indolo[1,2-*c*]quinazoline (**5**) to a side chain bearing a terminal group which can be cleaved homolytically to form a radical. The radical so formed could cyclize to give the seven membered lactam ring.

The gramine (**91**) was converted to indolo[1,2-*c*]quinazoline-12-acetic acid (**99**), the acid chloride of which was reacted with phenylselenoethylamine to give the selenium derivative (**100**).



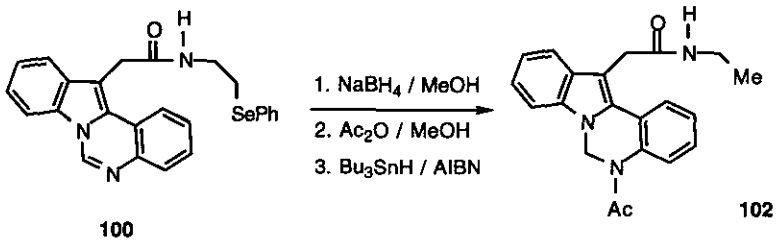
Scheme 35

However, the desired radical cyclization of **100** did not take place and the open chain product (**101**) was formed exclusively.



Scheme 36

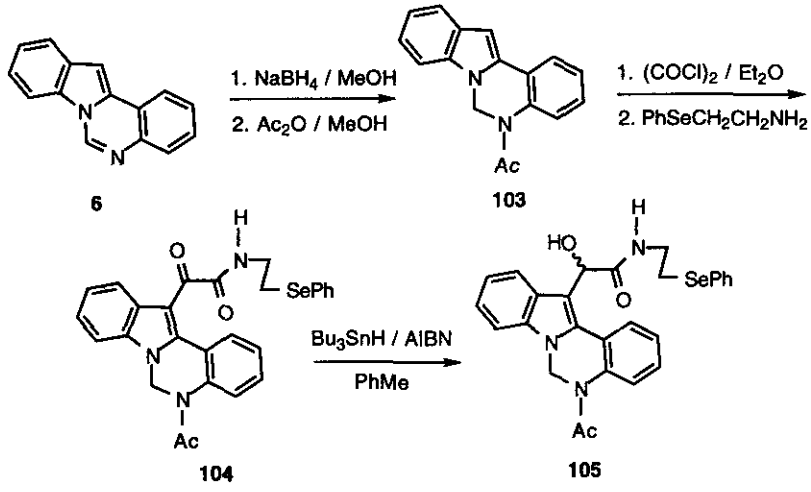
A variation of the reaction sequence was attempted by reducing the 5,6-double bond of **100** followed by protection of the basic nitrogen and attempted radical cyclization. Once again, only the open chain compound (**102**) was obtained.



100 102

Scheme 37

Modification of the side chain of **102** by synthesizing the keto derivative (**104**) afforded, after tin hydride reduction, only the alcohol (**105**).



6 103 104 105

Scheme 38

VI. ACKNOWLEDGMENT

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REFERENCES

1. C. O'Neill, *Chem. Ber.*, 1892, **25**, 461.
2. H. Machemer, *Chem. Ber.*, 1930, **63**, 1341.
3. A. Hantzsch, *Chem. Ber.*, 1921, **54**, 1221.
4. A. Hantzsch,*Chem. Ber.*, 1922, **55**, 3180.
5. G. Heller,*Chem. Ber.*, 1920, **53**, 1545.
6. G. Heller,*Chem. Ber.*, 1921, **54**, 2214.
7. G. Heller and W. Benade,*Chem. Ber.*, 1922, **55**, 1006.
8. G. Heller, *Chem. Ber.*, 1922, **55**, 2681.

9 . C. W. Bird, *Tetrahedron,* 1963, **19**, 901.
10. J. W. Cornforth, *J. Chem. Soc., Perkin Trans.1*, 1976, 2004.
11. K. Butler, M. W. Partridge, and J. A. Waite, *J. Chem. Soc.*, 1960, 4970.
12. R. Kikumoto and T. Kobayashi,*Tetrahedron*, 1966, **22**, 3337.
13. P. Friedlander and N. Roschdestwensky, *Chem. Ber.*, 1915, **48**, 1841.
14. C. C. Bond and M. Hooper, *J. Chem. Soc. C,* 1969, 2453.
15. E. E. Garcia, A. Arfaei, and R. I. Fryer, *J. Heterocycl. Chem.*, 1970, 1161.
16. A. K. Sen, S. B. Mahato, and N. L. Dutta, *Tetrahedron Lett.*, 1974, 609.
17. W. Schindler and H. Zähner, *Arch. Microbiol.*, 1971, **79**, 187.
18. W. Fedeli and F. Mazza, *J. Chem. Soc., Perkin Trans. 2,* 1974, 1621.
19. J. Bergman, B. Egestad, and J. O. Lindström,*Tetrahedron Lett.*, 1977, 2625.
20. M. Y. Jarrah and V. Thaller, *J. Chem. Res. (S)*, 1980, 186.
21. G. Honda, M. Tabata, and M. Tsuda, *Planta Medica*, 1979, **37**, 172.
22. G. Honda and M. Tabata, *Planta Medica*, 1979, **36**, 85.
23. G. Honda, V. Tosirisuk, and M. Tabata, *Planta Medica*, 1980, **38**, 275.
24. J. Bergman, J. O. Lindström, and U. Tilstam,*Tetrahedron*, 1985, **41**, 2879.
25. H. Karpf and H. Junek, *Tetrahedron Lett.*, 1978, 3007.
26. J. Y. Becker, E. Shakkour, and J. A. R. P. Sarma, *J. Chem. Soc., Chem. Commun.*, 1990, 1016.
27. J. Y. Becker, E. Shakkour, and J. A. R. P. Sarma, *J. Org. Chem.*, 1992, **57**, 3716.
28. S. Eguchi, H. Takeuchi, and Y. Matsushita, *Heterocycles,* 1992, **33**, 153.
29. M. Akazome, T. Kondo, and Y. Watanabe, *J. Org. Chem.*, 1993, **58**, 310.
30. E. Giovannini and P. Portmann, *Helv. Chim. Acta*, 1948, **31**, 1361.
31. A. Schönberg, R. Moubasher, and A. Mostafa, *J. Chem. Soc.*, 1948, 176.
32. W. Langenbeck, *Chem. Ber.*, 1927, **60**, 930.
33. W. Langenbeck and K. Weissenborn, *Chem. Ber.*, 1939, **72**, 724.
34. J. Bergman and U. Tilstam, *J. Chem. Soc., Perkin Trans. 1*, 1987, 519.
35. J. Bergman and U. Tilsam, *Tetrahedron*, 1985, **41**, 2883.
36. E. Fiedler, H. P. Fiedler, A. Gerhard, W. Keller-Schierlein, W. A. König, and H. Zähner, *Arch. Microbiol.*, 1976, **107**, 249.
37. J. Martinet and M. J. Grosjean, *Rev. Gen. Matiéres Colorantes*, 1922, **28**, 3.
38. J. Ch. Zou and L. Huang, *Acta Pharm. Sinica*, 1985, **20**, 45.
39. J. Bergman, *Phytochemistry*, 1989, **28**, 3547.
40. H. Laatsch and H. Ludwig-Köhn, *Liebigs Ann. Chem.*, 1986, 1847.
41. S. Mantegani, T. Bandiera, E. Brambilla, and G. Traquandi, *J. Heterocycl. Chem.*, 1992, **29**, 455.
42. J. R. Boissier, *Pharmacology*, 1978, **16**, 12.
43. E. Brambilla, E. Di Salle, G. Briatico, S. Mantegani, and A. Temperilli, *Eur. J. Med. Chem.*, 1989, **24**, 421.
44. R. Mordmann and T. Petcher, *J. Med. Chem.*, 1985, **25**, 367.

45. H. Ahgiin, U. Hollstein, and L. Hurwitz, *J. Pharm. Sci.*, 1988, **77**, 735.
46. J. A. Moore, C. J. Sutherland, R. Sowerby, E. G. Kelly, S. Palermo,and W. Webster, *J. Org. Chem.*, 1969, **34**, 887.
47. A. K. Kiang, F. G. Mann, A. F. Prior, and A. Topham, *J. Chem. Soc.*, 1956, 1319.
48. B. Robinson and M. U. Zubair, *Tetrahedron*, 1973, **29**, 1429.
49. R. L. Duncan, G. C. Helsley, and R. F. Boswell, *J. Heterocycl. Chem.*, 1973,**10**, 65.
50. F. Gatta and F. Ponti, *Boll. Chim. Farm.*, 1981, **120**, 102 (Ital.).
51. J. Bergman, R. Carlsson, and B. Sjöberg, *J. Heterocycl. Chem.*, 1977, **14**, 1123.
52. V. I. Shvedov, G. N. Kurilo, A. A. Cherkasova, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1975, 1096 (Russ.).
53. V. I. Shvedov, G. N. Kurilo, A. A. Cherkasova, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1977, 377 (Russ.).
54. G. N. Kurilo, S. Yu. Ryabova, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1979, 832.
55. A. N. Grinev, G. N.Kurilo, A. A. Cherkasova, M. D. Mashkovskii, N. I. Andreeva, and I. K. Sokolov, *Khim.-Farm. Zh.*, 1978, **12**, 97 (Russ.).
56. S. Yu. Ryabova, A. N. Grinev, and L. M. Alekseeva, *Khim. Geterotsikl. Soedin.*, 1988, 668 (Russ.).
57. P. Molina, M. Alajarin, and A. Vidal, *Tetrahedron*, 1990, **46**, 1063.
58. J-Y. Mérour and L. Savelon, *Heterocycles*, 1991, **32**, 849.
59. R. L. Duncan, *Ger. Offen.* 2,051,961; Apr. 25, 1975 (*Chem. Abstr.*, 1971, **75**, 36115d).
60. V. I. Shvedov, A. N. Grinev, G. N. Kurilo, and A. V. Cherkasova, *U.S.S.R.* 481,613; Aug. 25, 1975 (*Chem. Abstr.*, 1976, **84**, 17409x).
61. V. I. Shvedov, G. N. Kurilo, A. V. Cherkasova, and A. N. Grinev, A.N.; *U.S.S.R.* 539,885; Dec. 25, 1976 (*Chem. Abstr.*, 1977, **86**, 155692b).
62. G. N. Kurilo, S. Yu. Ryabova, and A. N. Grinev, *U.S.S.R.* 690,017; Oct. 5, 1979 (*Chem. Abstr.*, 1980, **92**, 76545b).
63. A. N. Grinev and S. Yu. Ryabova, *U.S.S.R. SU* 816,116; Dec. 30, 1985 (*Chem. Abstr.*, 1986, **105**, 208906u).
64. A. J. Blackman, T. W. Hambley, K. Picker, W. C. Taylor, and N. Thirsasana, *Tetrahedron Lett.*, 1987, **28**, 5561.
65. N. Barnwell, R. L. Beddoes, M. B. Mitchell, and J. A. Joule, *Heterocycles*, 1994, **37**, 175.
66. A. D. Billimoria and M. P. Cava, *J. Org. Chem.*, 1994, **59**, 6777.

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