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Some Newer Aspects of Plant Alkaloids†

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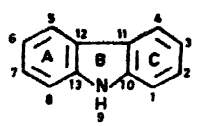
THE alkaloid bearing plants as sources of medicine and toxic materials made important contributions to the society from the beginning of community life and agricultural mode of production in human civilisation. *Papavera somnifera*, the source of opium, provided the anodyne of choice even 6000 years ago. The toxic plant constituents also found use in the state management[1]. Since the isolation of the first alkaloid morphine[2] in 1904 from opium there has been widespread interest in the search for alkaloids from toxic and other plants known to be useful in indigenous medicine of different countries. This *pragmatic* approach paid the world a good dividend. Nearly 3000 alkaloids classified into 58 groups have been known till 1960[3]. Some of them are medicines of choice, some are important from forensic considerations and some have very interesting structural complexities.

Today alkaloids are also known for their alleochemic and ecological functions[4,5]. Human endeavours spread over more than a century have been necessary to elucidate the structures of some complex alkaloids like strychnine, morphine and many others.

In India Shaugnessey[6] of Calcutta Medical College started from *pragmatic* considerations, the isolation of active principles of Indian Medicinal Plants as early as in 1840. But the first world-wide recognition of Indian alkaloidal investigations was in the area of pharmacology when quinine was accepted as an official remedy of malaria by League of Nations due to the investigations of R. N. Chopra at the School of Tropical Medicine in the twenties of this century[6]. The discovery of the pharmacologically active alkaloids of *Rauwolfia serpentina* in 1931 by Siddique and Siddique[7] could be considered as the beginning of isolation and structure elucidation work on alkaloids in India. Siddique's work attracted attention from all over the world on Indian alkaloidal studies. Indian alkaloidal investigations initiated by B. B. Dey at Madras and P. K. Bose at Calcutta, received world-wide appreciation due to extensive and fruitful work of T. R. Govindachari at Madras and Bombay and Asima Chatterjee at Calcutta. Their contributions resulted into structure elucidations of various interesting and pharmacologically significant compounds. Some of them like nareline[9] (1), grandifoline[8] (2) and teliacorine/teliacorinine[10] (3) are structurally novel. Some alkaloidal work was also reported by R. N. Chakravarti in the fifties of this century from Calcutta School of Tropical Medicine.

While the majority of the studies on alkaloids in India is based on *pragmatic* approach. we have been interested in the biological approach to such investigations (micromolecular taxonomic approach) since 1960. The placement of the family Rutaceae in the order Rutales by Hutchinson[11] in his Lignosae attracted our attention to the investigations on the alkaloidal profile of the members of Rutaceae which abounds in alkaloids derived from anthranilic acid[12]. In such effort, we discovered in 1962. the first member of the then unknown 'Carbazole Alkaloids'. Different aspects of this new group of alkaloids form the subject-matter of this presentation.

Murravanine, the first member of the group, was isolated by the present author from *Murraya koenigii* Spreng. before 1962. In 1962, he could ascertain that murravanine was a carbazole derivative having a formyl and methoxy group from its ^1H nmr spectrum and other data at hand. Evidently it was the first carbazole of biological origin discovered ninety years after the discovery of the parent compound carbazole (4) from coal tar in 1872 by Graebe and Glazer[13]. Its structure was established by degradation[14] and synthesis[15] by us as 5. In working out the structures of various alkaloids, the uv spectral data of formyl-[16] and methoxycarbazoles[17] were helpful in locating the position of the formyl and methoxy groups on the carbazole skeleton[18]. Though Basu[19] could not reconcile the experimental uv data of methoxycarbazoles with theoretical calculations, the uv data of methoxycarbazoles or their congeners have been successfully utilised in assigning the structures of



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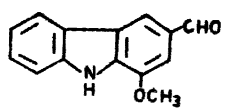

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carbazole alkaloids[18] as well as in their synthesis.

Like many alkaloids of Rutaceae, murrayanine (5) has the anthranilic acid pattern. To provide further credence to the anthranilate origin of carbazole alkaloids, we looked for these alkaloids in taxonomically related *Glycosmis pentaphylla* Retz.

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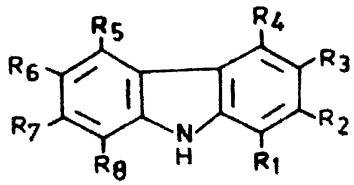


(6) $R_1 = R_2 = R_4 = R_5 = R_7 = R_8 = H$, $R_3 = CH_3$, $R_6 = CH_3O$

(7) $R_1 = R_4 = R_5 = R_7 = R_8 = H$, $R_2 = R_6 = OCH_3$, $R_3 = CH_3$

(16) $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_8 = H$, $R_3 = CH_3$

(17) $R_1 = R_7 = R_8 = OCH_3$, $R_2 = R_4 = R_5 = R_6 = H$, $R_3 = CH_3$

(18) $R_1 = R_4 = R_5 = R_6 = H$, $R_2 = R_7 = OCH_3$, $R_3 = CH_3$, $R_8 = CHO$

(19) $R_1 = R_4 = R_5 = R_7 = R_8 = H$, $R_2 = OH$, $R_3 = CHO$, $R_6 = OCH_3$

(21) $R_1 = Ph$, $R_2 = CH_3$, $R_3 = OCH_3$, $R_4 = R_5 = R_6 = R_7 = R_8 = H$

(22) $R_1 = Ph$, $R_2 = CH_3$, $R_3 = OCH_3$, $R_4 = R_5 = R_7 = R_8 = H$, $R_6 = Cl$

(23) $R_1 = R_2 = CH_3$, $R_3 = R_4 = OCH_3$, $R_5 = R_6 = R_7 = R_8 = H$

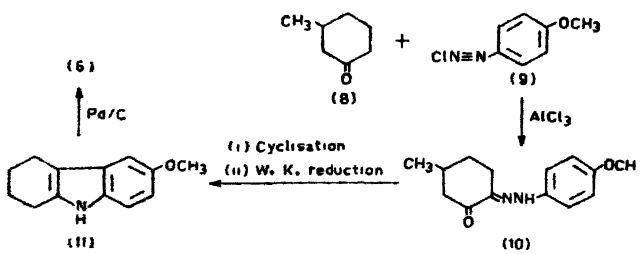
(24) $R_1 = R_2 = CH_3$, $R_3 = OCH_3$, $R_4 = OH$, $R_5 = R_6 = R_7 = R_8 = H$

(25) $R_1 = CHO$, $R_2 = CH_3$, $R_3 = OCH_3$, $R_4 = OH$, $R_5 = R_6 = R_7 = R_8 = H$

(26) $R_1 = CHO$, $R_2 = CH_3$, $R_3 = R_6 = OCH_3$, $R_4 = OH$, $R_5 = R_7 = R_8 = H$

D.C.[18,20]. (Fam. : Rutaceae ; Sub-fam. : Aurantoidae) which is known to elaborate alkaloids derivable from anthranilic acid, i.e. furoquinolines, acridones and quinazolones. Glycozoline (6) and glycozolidine (7) were isolated from the root bark of *G. pentaphylla* by us.

The structure of glycozoline was confirmed by synthesis using Borsche method of synthesis of carbazoles as well as by taking recourse to the synthesis of hydrazone for the tetrahydrocarbazole synthesis by Japp-Klingemann reaction[18]. Recently we have used Lewis acid catalysed aliphatic diazocoupling[21] of 3-methylcyclohexanone (8) with *p*-methoxybenzene diazonium chloride (9) to synthesise the hydrazone (10) required for tetrahydrocarbazole (11) formation to effect the synthesis of glycozoline.

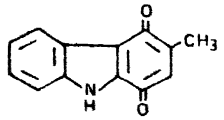


The report of aromatisation and dehydrogenation of acyclic hydrocarbons with elemental iodine at an elevated temperature by Raley *et al.*[22] promoted us to synthesise carbazole by dehydrocyclisation of diphenylamine in presence of iodine in a sealed tube at 350°. Carbazole (4), 3-methylcarbazole (16), glycozolidine (7)[23] and glycozoline (6)[18] have been synthesised using diphenylamine (12), 3'-methyldiphenylamine (13), 3,4'-dimethoxydiphenylamine (14) and 4-methyl-4'-methoxydiphenylamine (15) respectively.

In the dehydrocyclisation method of carbazole synthesis Graebe and Glazer[18] used red-heat temperature only, while Zelinsky[24] used palladium acetate as catalyst. Jackson and Sasse[25] used degassed Raney nickel to effect the cyclisation with lesser yield than that reported by Zelinsky. We also used degassed Raney nickel for synthesis of the alkaloids[26]. After our work[23] further modification of experimental conditions of cyclisation have been made by several workers. At present the method has been much more popular[27]. The concept of radical cyclisation of diphenylamine to carbazole at high temperature advocated by Chakraborty[18] has gained further ground by the report of Bhattacharyya and Jash[28] when they used benzoyl peroxide in CCl_4 as the reagent. The photolytic and anodic methods have also been used to effect cyclodehydrogenation of diphenylamine to carbazole[18].

Murrayastine[29] (17), murrayaline[29] (18), lansine[30] (19) are some of the newer additions to the tricyclic alkaloids after 1980[31]. Some newer plant isolates, like mukonal, 2-methoxy-3-methylcarbazole, 2-hydroxy-3-methylcarbazole, glycozolinine, koeniline, murrayafoline A, glycozolidal however have been identified[32] with already known structures of carbazoles. Furukawa *et al.*[33] used NOE by irradiation of methyl and methoxy groups to locate the appropriate protons on a tricyclic system. Oxidative

variants of ring-C of carbazole alkaloids like murrayaquinone A[88] (20) have also been reported.



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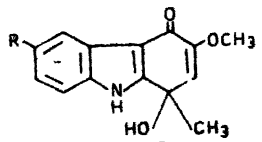
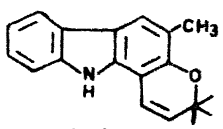
Closely related to the structures of these tricyclic alkaloids are some alkaloids from the members of lower plants. Hyellazole[84] (21) and its chloro derivative (22) were isolated from marine alga *Hyella caespitosa* by Cardellino II *et al.* The antibiotics of carbazomycin group (23–28) and 6-methoxy analogues of 23 and 24 were reported from *Streptoverticillum ehminse* by Nakamura *et al.*[85] as well as by Kondo *et al.*[86] In the structure



(27) R = H, (28) R = OCH_3

determination of carbazomycinal (25) Muramo *et al.*[86] used LSPD method for assignment of ring-A carbons of carbazomycinal. Carbazomycin-G (27) and H (28) are interesting variants of ring-C of carbazomycin B (24).

Girinimbine[87,18] (29), the first member of C-18 alkaloids with till then unknown pyranocarbazole skeleton, was reported[87] by us in 1964 from *Murraya koenigii* Spreng. The mass spectrum of girinimbine showed the high intensity carbazolopyrilim ion at *m*/z 248 (*M*-15) (30). This characteristic ionic species (30) or it congeners have extensively been utilised in structure elucidation of various alkaloids of C-18 or C-23 skeletons with a pyranocarbazole fragment like girinimbine. Compounds with saturated pyran ring like that in dihydrogirinimbine (31) gives a mass spectral peak at *m*/*z* 210 represented by the ionic species (32).



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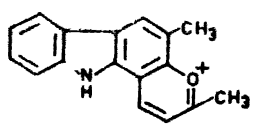
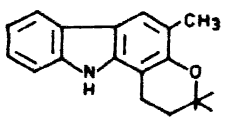


(30) m/z 248



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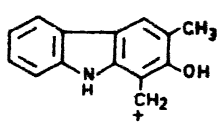
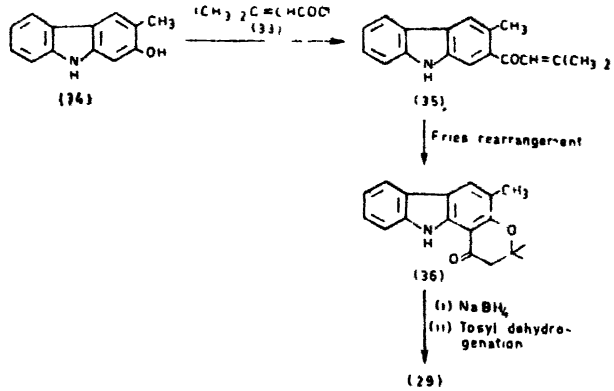
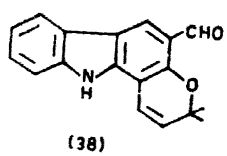


(32) m/z 210

From the degradation and spectral studies the structure 29 was assigned to girinimbine[18] which was confirmed by three syntheses[18]. In our synthesis[18] we condensed β,β-dimethylacrylyl chloride (33) with 2-hydroxy-3-methylcarbazole (34) at 5° to form the acylcarbazole (35) which on Fries rearrangement and cyclisation gave the chromamone (36). This on borohydride reduction and dehydrotosylation furnished (29). Kurreel *et al.*, on the other hand obtained 29 by refluxing 3-hydroxyisovaleraldehyde dimethyl acetal (37) with 34 in 10% yield. Narashimhan on the other hand condensed sodium salt of 1-formyl-2-hydroxy-3-methylcarbazole with α-methyl allyl triphenyl phosphonium chloride to obtain 29 with much poorer yield.



Murrayacine (38) an oxidative variant of girinimbine was also isolated from *M. koenigii* Spreng. by us whose structure was established from its physical data and total synthesis as well as by DDQ oxidation of 29[18].



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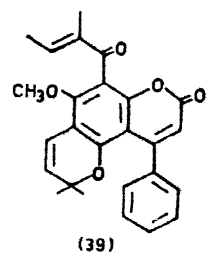

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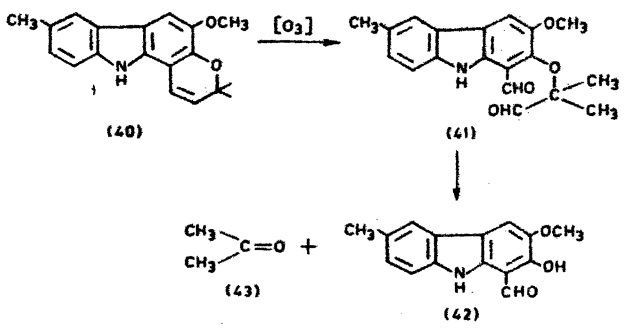
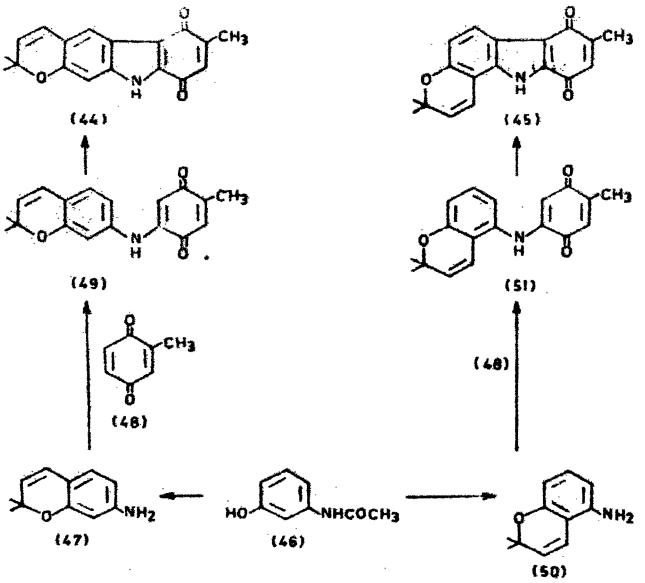
Ozonisation of coumarins and alkaloids containing 2,2-dimethyl-Δ^3-pyran ring was considered to be abnormal by Polonosky[88]. It was considered that first there was migration of the pyran double bond and subsequent attack of ozone leading to the degradation products like acetaldehyde and acetone from callophylloide (39). From our experiments with heptazolidine (40), it has been shown that ozonisation of 2,2-dimethyl-Δ^3-pyran fused to an aromatic system follows normal pathway. Heptazolidine[18] furnished a dialdehyde (41), an α-hydroxy aldehyde (42) and acetone (43). This idea has also been supported by ozonisation experiments on mahanimbine reported by Joshi *et al.*[18].

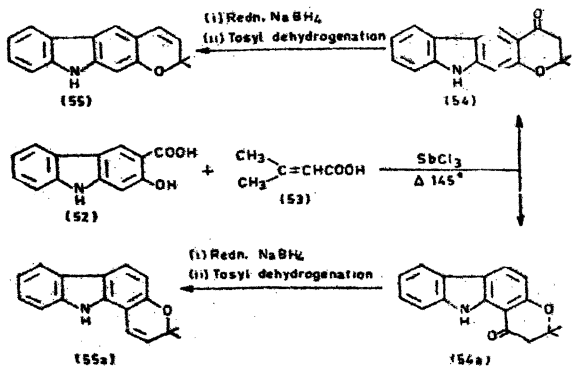
Recent interesting addition to the pyranocarbazole alkaloids are the pyranoquinone A (44) and pyranoquinone B (45)[89]. The structures of which



have been confirmed by synthesis through the diphenylamine route as shown below.

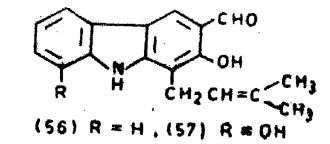


7-Amino-2,2-dimethylchromene (47) prepared from *m*-hydroxyacetamide (46) on condensation with 2-methyl-1,4-benzoquinone (48) gave the diphenylamine (49), which on cyclisation afforded (44). Similarly, 5-amino-2,2-dimethylchromene (50) on condensation with 48 afforded 51, which on subsequent cyclisation gave 45. The above results prompted us to report[40] the thermal synthesis of norgirinimbine and its linear isomer accomplished earlier in our laboratory[41].



2-Hydroxycarbazole carboxylic acid (52) on treatment with β,β-dimethylacrylic acid (53) at 145° in presence of $SbCl_5$ furnished the chromanones (54 and 54a). Both the chromanones on reduction and tosyl dehydrogenation furnished respectively the linear 2,2-dimethyl-Δ^8-pyranocarbazole (55) and its regio-isomer norgirinimbinine (55a). Compound 55 is the first linear pyranocarbazole to be reported.

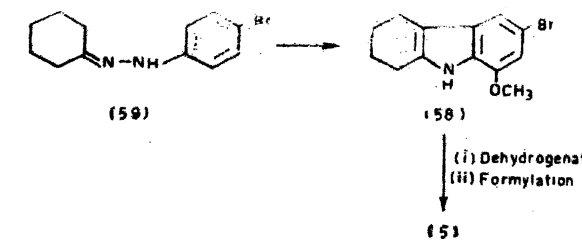
Our publications from 1964–1966 on grinimbine, murrayanine, glycozoline, glycozolidine and mahanimbine attracted immediate attention of the Indian Chemists, as such the first carbazole alkaloid with γ,γ-dimethylallyl chain and probable pecursor of girinimbine, heptaphylline (56) was reported from *Clausena heptaphylla*[42] which we were examining for carbazoles from taxonomic considerations. We also reported[43] heptazoline (57) from the plant.



(56) R = H, (57) R = OH

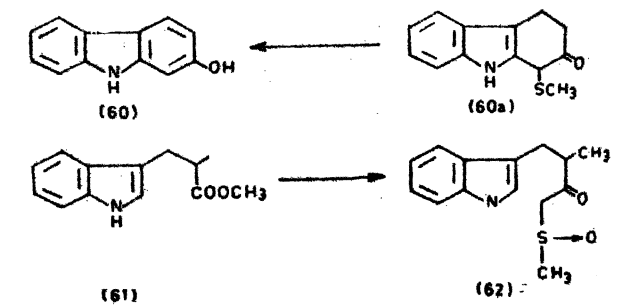
The novelty of the structures and biological properties of carbazole alkaloids attracted the attention of chemists all over the world for their synthesis.

Crum and Sprague[44] synthesised murrayanine. They obtained 3-bromo-1-methoxy-5,6,7,8-tetrahydrocarbazole (58) from 2-methoxy-4-bromophenylhydrazone of cyclohexanone (59). 58 on dehydrogenation and subsequent reaction with formanilide yielded 5.

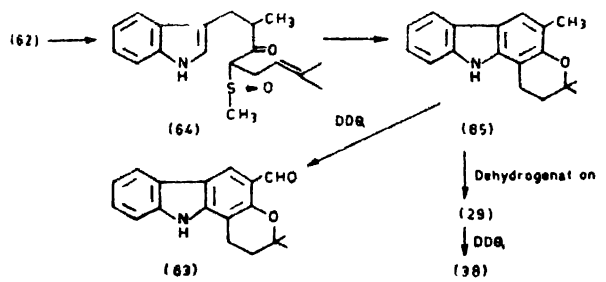


Carruthers[45] synthesised glycozoline by photolytic cyclodehydrogenation of (15).

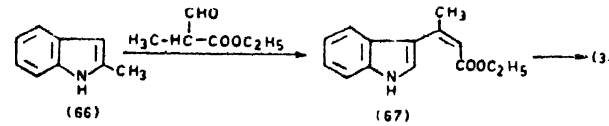
Oikawa and Youmitschi[46] used their ketosulphoxide method to synthesise 2-hydroxycarbazole (60), girinimbine (29), murrayacine (38) and cycloheptaphylline (63). The ester (61) was treated with sodium methylsulphinylmethide to give quantitatively a ketosulphoxide (62).



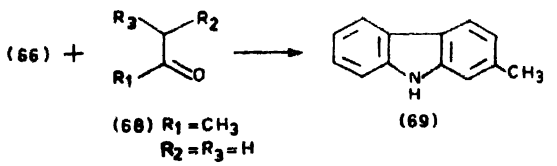
Alkylation of **62** with prenyl bromide in presence of potassium hydride gave **64**. When **64** was heated with *p*-toulene sulphonyl chloride in accetonitrile dihydrogirinimbine (**65**) was obtained. **65** on dehydrogenation gave girinimbine (**29**) which on oxidation with DDQ afforded murrayacine (**38**). On DDQ oxidation **65** gave **63**.



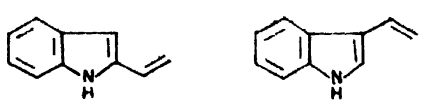
Bergman and Carlson[47a] reported the synthesis of 2-hydroxy-3-methylcarbazole (**34**) using 2-methylindole (**66**) and 2,3-unsaturated carbonyl compound by alkylation at 3-position of indole (**67**).



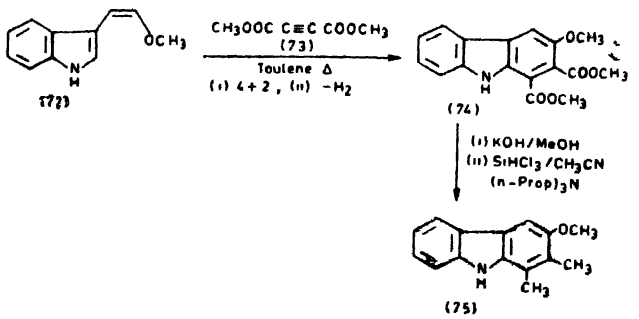
Better yields of the carbazoles like **69** have been reported by Bergman and Pelcman[47b] using 2,3-unsaturated-ketones (**68**) and 2-alkyl-substituted-indole in presence of Pd/C. The use of molecular sieve in the reaction mixtures have been found to increase the yield.



The occurrence of 3-vinylindole system in carbozomycin, girinimbine and pyridocarbazoles, provided some incentive to Akgun and Pindur[48] to investigate the synthesis of carbazoles using 3-vinylindole as a building block. Selectively functionalised 2- and 3-vinylindoles (**70** and **71**) represent 4π-components and synthetically attractive building blocks for the synthesis of carbazole alkaloids. 2,3-Vinylindoles have 1-aminobutadiene structural features imbeded in a hetrocyclic system. The addition of dienophile to vinylindoles have extensively been utilised for building tricyclic and polycyclic carbazole systems[49,50].

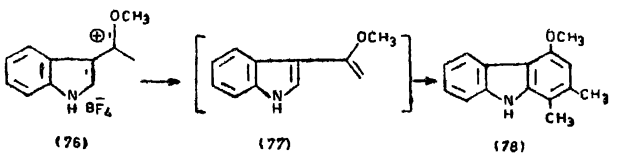


In some cases newer heteroatoms have been introduced in the heterocyclic system. The subject has been reviewed by Pindur[49,50]. Reactions involved (4+2) cycloaddition under various experimental conditions with varying yields. The syntheses so far reported embrace few of the naturally occurring carbazole alkaloids probably due to their specific substitution pattern. The syntheses of 4-demethoxycarbazomycin[51] and its regio-isomers[52] are interesting illustrations of application of 3-vinylindoles.



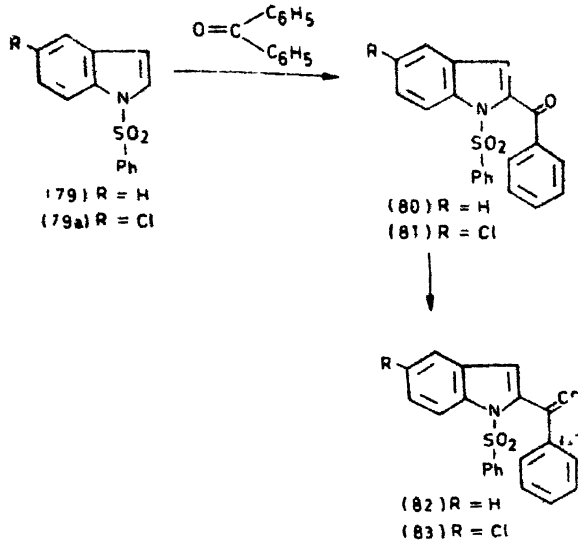
The (4+2) cycloaddition of **72** with dimethyl acetylene dicarboxylate (**73**) and dehydrogenation of the cyclo-adduct gave **74**. Hydrolysis of **74** and subsequent reduction furnished **75**.

The regio-isomer 3-demethoxycarbazomycine[50] was prepared starting from indolyl(methoxy)methylcarbenium tetrafluoroborate (**76**) which was deprotonated *in situ* to reactive (N-unprotected) 3-vinylindole (**77**) which on (4+2)cycloaddition reaction with acetylene dicarboxylic acid and subsequent dehydrogenation gave the 3-demethoxycarbazomycin (**78**).

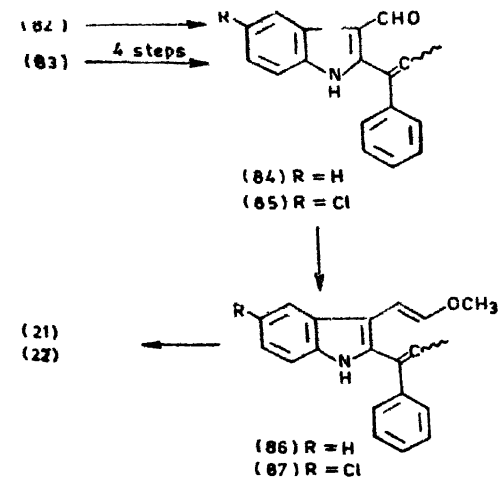


The synthetic potential of 2-vinylindoles have been explored[47] to a great extent in spite of the fact that they are much less reactive than 3-vinylindoles. The syntheses of hyellazole and chlorohyllazole[53,54] constitute elegant illustrations of synthesis involving 2-vinylindoles.

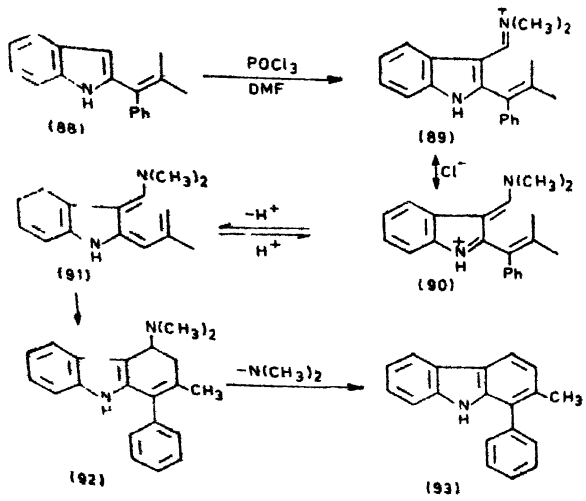
Condensation of *N*-phenylsulphonyl indole (**79**) or its chloro derivative (**79a**) with benzoic anhydride afforded **80** or **81**, which on Wittig reaction gave 2-(1'-phenyl-1'-propenyl)indole (**82**). On Vilsmier reaction **82** furnished the formyl derivative (**84**) while the required formyl derivative (**85**) in case of **83** was obtained by treatment of **83** with oxalyl chloride and subsequent esterfication, hydrolysis and dicarboxylation. Both **84** and **85** on Wittig reaction furnished the methoxyvinyl compounds (**86** and **87**). The divinylindole derivatives (**86** and



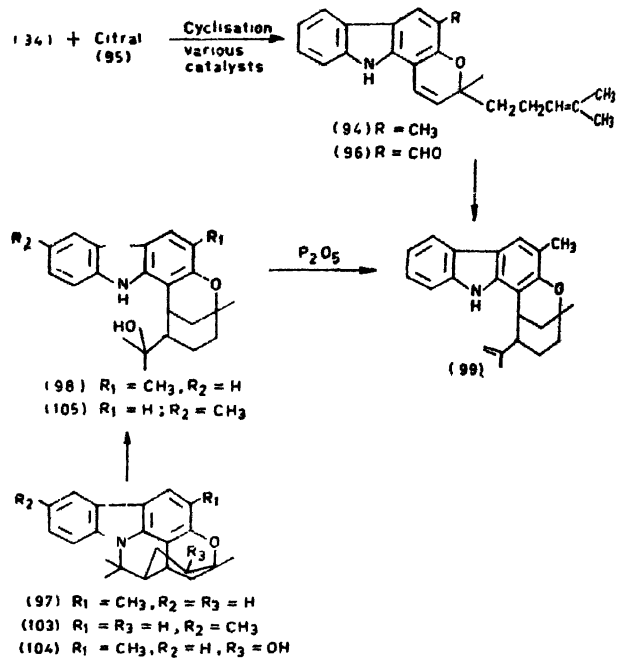
87) on thermolysis furnished hyellazole and chlorohyellazole.



Bergman *et al.*[47b] synthesised 3-demethoxyhyellazole using 2-vinylindole as the substrate. However they took altogether different route to such synthesis.



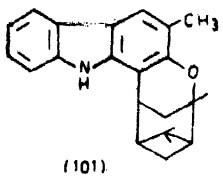
Mahanimbine, $C_{28}H_{25}NO$, m.p. 94–95° (M^+ 331), $[\alpha]_D^{CHCl_3}$ +45.1, the first member of carbazole alkaloids with C-23 carbon skeleton, was reported[55] by us from *M. koenigii* Spreng. We reported the part structure built on a pyranocarbazole of C-18 group-like with C_5H_8 residue containing a double bond. While our work was in progress, Narashimhan[56] reported its structure as **94** which was readily confirmed by us and other workers[18,57] using the method[58] of terpenic cyclisation with 2-hydroxy-3-methylcarbazole (**34**) with citral (**95**).



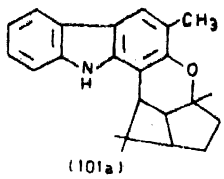
The formyl analogue of mahanimbine, murrayacinine was shown to have the structure **96** by degradation and synthesis[18]. Murrayazoline (**97**), murrayazolinine (**98**) and murrayazolidine (**99**) are interesting cyclomers isolated by us. The *dl*-murrayazoline, named mahanimbidine (**100**) and curryangine[18] were isolated respectively by Kureel *et al.* as well as by Wadia *et al.* The isolation of the optical antipode of murrayazoline was reported by Furukawa *et al.*[58]. The structure of murrayazoline was confirmed by *X*-ray crystallographic studies while the structure of mahanimbidine determined by physical data. Due to strained ring system in murrayazoline it undergoes facile acid catalysed N–C bond cleavage leading to the formation of murrayazolinine. Sluggish N–C bond cleavage had also been reported by Patel[59] with mahanimbidine isomers. This N–C bond cleavage reaction has given access to the understanding of the interrelationship[18] between murrayazoline, murrayazolinine and murrayazolidine as murrayazolinine after P_2O_5 dehydration afforded murrayazolidine. Bandernayake *at al.*[60] synthesised it from mahanimbine by passing mahanimbine over Dowex 50×8 (H^+) resin.

Bicyclomahanimbine, an interesting cyclomer of mahanimbine, was isolated by Kapil *et al.* and

proposed its structure as **101**[18] while Crombie from the analogy of the *X*-ray crystal structure of cannabicyclol proposed the structure as **101a**[18]. The structure of **101a** was supported by our synthetic

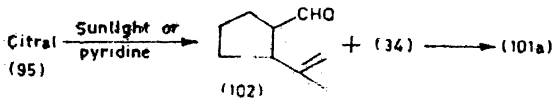


(101)

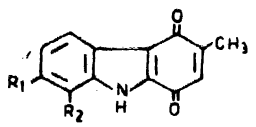


(101a)

experiments when 2-hydroxy-3-methylcarbazole (**34**) on condensation with photocitral A (**102**) furnished bicyclomahanimbine (**101**).

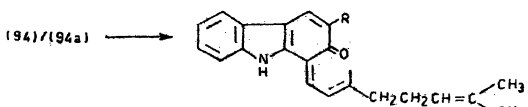


New additions to cyclomers of C-23 alkaloids, like mahanimbine, are naturally occurring isomurrayazoline[61] (**103**), murrayazolinol[62] (**104**) and acid-catalysed hydration product isomurrayazolinine (**105**). Carbazoloquinones[58] of C-18 and C-23 skeleton murrayaquinone-B (**106**), –C (**107**) and –D (**108**) are novel additions to these alkaloids.



(106) R_1 = OCH_3, R_2 = DMA
(107) R_1 = OCH_3, R_2 = Geranyl chain
(108) R_1 = OH, R_2 = Geranyl chain

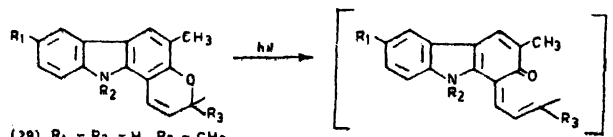
Mahanimbine racemises in a sealed tube at 200° as well as at 90° in an isooctane solution in dark. The racemisation has been rationalised by enone-chromene (**109**) transformation and subsequent ring closure. The incorporation of deuterium at C-10 and C-4 in the enone isomer (**109a**) of normahanimbine (**94a**) has been cited as a supportive evidence by Bandernayake *et al.*[60]. Chakraborty[68] have shown that mahanimbine on standing in etha-



(109) R = CH_3
(109a) R = H

nolic solution in darkness undergoes optical inversion for +45° to –24.8°. Attempt to isolate the *l*-form by evaporating the solvent resulted only in the isolation of *dl*-form. The recovery of parent chromene[64] after removal of the solvent in photolysis product of chromene (**110**) could be cited as a relevant interesting finding. Padwa and Lee[64] showed that during the photolysis of chromene in methanol, methanol addition (**111**) took place which readily reverted to the parent chromene on removal of the solvent.

In consideration of interesting rearrangement involving quinolide intermediates of the pyranocarbazoles, we examined the photolytic transformation[65] of some pyranocarbazoles (**29, 94, 112-116**). Benzene solutions of the compounds were irradiated at room temperature by low or medium pressure mercury vapour lamp (16 W – 254 nm or 400 W – 360 nm) under nitrogen atmosphere and subsequent work-up yielded the products (**117 – 122**). The *N*-sulphonyl derivative (**116**) however did not provide any photo-product.



(29) R_1 = R_2 = H, R_3 = CH_3
(94) R_1 = R_2 = H, R_3 = $CH_2CH_2CH=C(CH_3)_2$
(112) R_1 = OCH_3, R_2 = H, R_3 = CH_3
(113) R_1 = H, R_2 = $CH_2CH=CH_2$, R_3 = CH_3
(114) R_1 = H, R_2 = R_3 = CH_3
(115) R_1 = H, R_2 = C_2H_5, R_3 = CH_3
(116) R_1 = H, R_2 = SO_2CH_3, R_3 = CH_3

(29a, 94a, 112a – 115a)

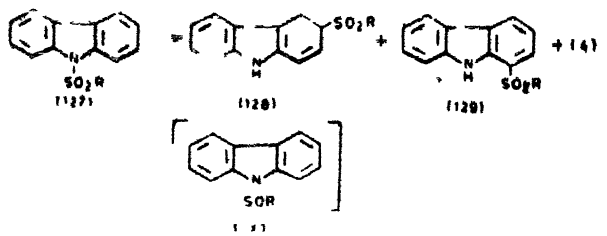
(124) R_1 = H, R_2 = CH_3
(125) R_1 = H, R_2 =
(126) R_1 = H, R_2 = C_2H_5

(117 – 122)
R_1, R_2, R_3 same as (29, 94 and 112 – 115)

The genesis of the photo-products (**118 – 123**) could be rationalised by the formation of *o*-quinoeallide type intermediates (**29a, 94a, 112a – 115a**) as envisaged by Padwa and Lee. Subsequently it undergoes and recyclises to 2,5-dihydro-oxepinocarbazole from pyranocarbazole substrate involving a 1,4-shift. The probable participation of the nitrogen lone-pair in the overall process has been envisaged as the *N*-sulphonyl derivative did not produce any rearranged product. Both the sensitised and unsensitised photolysis of some *N*-substituted-oxipinocarbazoles yielded the same *N*-substituted-bicyclooxipenocarbazoles (**124 – 126**). The production of the bicyclocarbazole could be explained due to the participation of the triplet excited stage which through the probable intermediates arising due to rearrangement similar to Zimmerman's di-π-methane rearrangement[67] or otherwise.

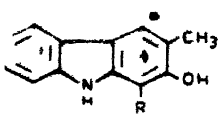
On the other hand, the phtochemical studies of sulphonyl carbazoles (**127**) resulted into the production of 1- and 3-sulphonylcarbazoles[66] (**128** and

129). The photochemically excited **127** underwent a fast homolytic cleavage of nitrogen–sulphur covalent bond, thereby generating the solvent-caged intermediate **130**. The formation of photo-products (**128** and **129**) could be rationalised by intramolecular 1,3- and 1,5-migrations of sulphonyl radical. Thus a true photo-Fries rearrangement hitherto not reported in the carbazole series has been demonstrated. *N*-Benzoylcarbazole did not undergo similar changes. This method provides an easy access to the synthesis of 1- and 3-sulphonylcarbazoles which

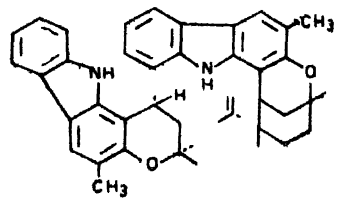


have been difficult to synthesise by the other methods. These compounds may be of biological importance.

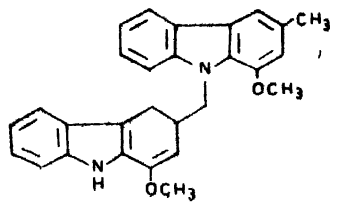
Previously proposed ideas[68] about the anthranilate and 3-methylcarbazole origin of carbazoles alkaloids of higher plants and the larger participation of 2-hydroxy-3-methylcarbazole in the formation of pyranocarbazoles have been further substantiated by the isolation of several derivatives of 3-methylcarbazole[68]. The occurrence of linear pyranocarbazolequinone[69] and the synthesis of linear pyranocarbazole[40] shows that linear pyranocarbazoles could arise when 3-position of the carbazole nucleus is unoccupied or occupied by a readily removable group. The isolation of murrayaline (**18**) with an additional one carbon supports the previously proposed idea that incorporation of one carbon into a preformed carbazole skeleton[69] may take place. Furkawa supported Chakraborty's idea about the anthranilate origin of carbazoles from the occurrence of murrayaline. Carbazoloquinones could be considered as an oxidative variant of alkaloids with hydroxyl at C-1 of ring-C. Mahanimbinol[70] (**131**) could be considered the precursor of mahanimbine group of alkaloids. From biomimetic oxidation studies of 3-methylcarbazole, Chakraborty *et al.*[51,71] predicted the occurrence of dimeric carbazole alkaloids in plants. The idea has been proved to be a reality by the discovery of murrafoline[72] (**132**) and several dimeric carbazole alkaloids like **132**–**137** from *M. euchrestifolia* by Furukawa *et al.*[73].



(131)
R = Geranyl chain



(132)



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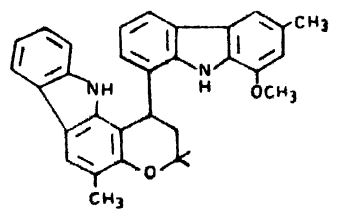

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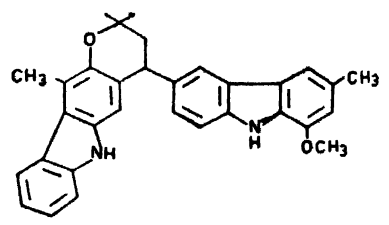

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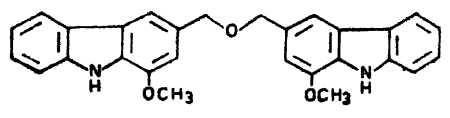

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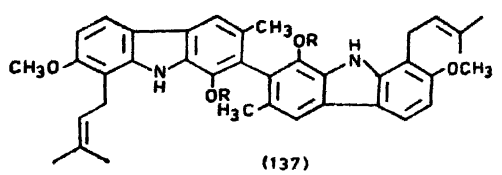
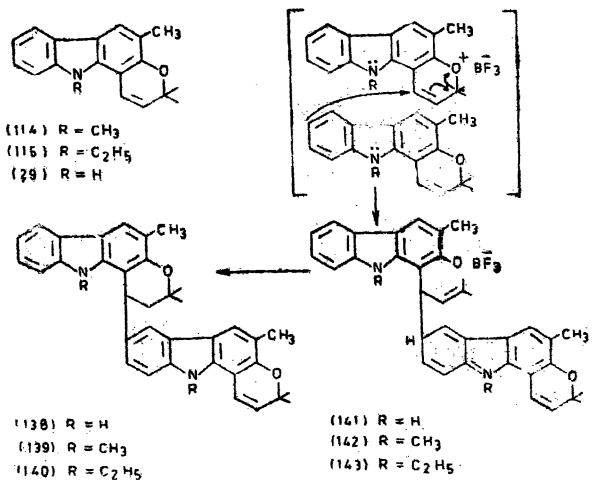


(137)

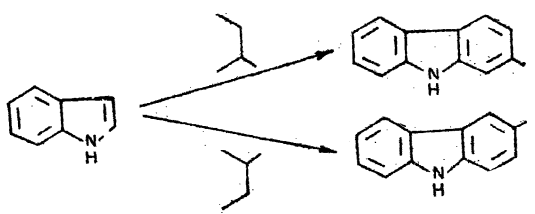
Murrafoline (**132**), the first biscarbazole with C-41 skeleton, has a murrayazolidine unit and a dihydrogirinimbine unit attached to position-8 of the carbazole unit. Such compounds with dihydrogirinimbine unit attached to positions-6 and -8 are known. Position-6 and -8 happen to be the relatively more active nucleophilic centres than position-5 and -7. It is likely that an electrophilic species with electrophilic centre at the benzylic position of the dihydrogirinimbine unit may attach

to position-6 or -8. Our experiments with girinimbine (**29**) and its *N*-methyl (**114**) and *N*-ethyl (**115**) derivatives under BF_3-Et_2O catalysed reaction resulted in isolation of the biscarbazoles (**138–140**) the formation of which could be explained through the intermediate of the type **141–143**.



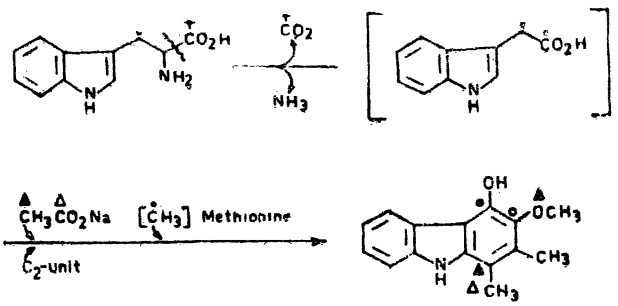
Our experiments provide a rationale for the attachment of the dihydrogirinimbine unit at 6/8-position in biscarbazoles of natural and synthetic origin as also the absence of attachment of such unit at 5- or 7-position. On this background, the attachment of 2,2-dimethylpyranoaromatic compounds to another aromatic substrate at the most active nucleophilic centre as in pyranoacridone, acronycine[75] may also be rationalised.

2-Methylcarbazole is a common skeletal unit of the alkaloids of lower plants. This could be conceived to arise from an indole unit and a mevalonate unit in a Scheme shown below.



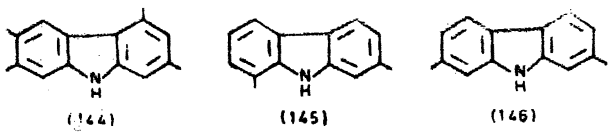
Such an idea though appears to be rational in consideration of the biogenetic ideas about the alkaloids of higher plants, it does not find support from the experimental results reported by Nakamura *et al.* on the biosynthesis of carbazomycin B as detailed in the Scheme 1[68,82].

Interestingly it may be mentioned that 2-methylcarbazole skeleton is the common structural features of several carbazoles isolated from the petroleum



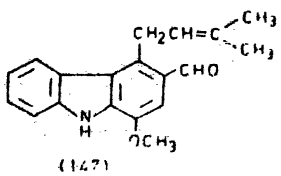
Scheme 1. Biosynthesis of carbazomycin B.

oil (**144–146**) obtained from the continental shelf of Kwait[76].



Taxonomic considerations :

The majority of the carbazole alkaloids have been reported from taxonimically related genera Murraya, Glycosmis and Clausena (Fam.: Rutaceae ; Sub-Fam. : Aurantoidae). Swingle segregrated these genera into subtribe Clausenae. The occurrence of the carbazole alkaloids in these genera is interesting from the standpoint of Swingle's segregatation. The genus Murraya appears to be varsatile in giving expression to the largest varieties of these alkaloids. The report of ekebergenine (**147**)[77] from the genus



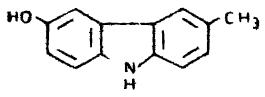
Ekebergia (Fam. : Meliaceae) calls for further investigations of carbazole alkaloids in Meliaceae as the closeness of the families Meliaceae and Rutaceae have been reflected in a members of nortriterpenes of limonin group[12b,78].

The occurrence of alkaloids in marine alga (Cynophyta) *Hyella caespitosa* and bacteria *Streptoverticillum ehimese* (Schizomicophyta) show that alkaloids could also be obtained from plants at advanced as well as in primitive phyletic status probably through separate biosynthetic pathway. Though the data at hand restrict broad discussion on the taxonomic implication of the alkaloids, Chakraborty[18] as well as Furukawa successfully utilised taxonomic considerations to isolate a large number of carbazole alkaloids.

Biological properties :

The importance of alkaloids of the group have been reflected in the various biological properties[18,81,82,68]. We[79] reported the antibiotic

properties of alkaloids as early as in 1965. The most active constituent was demethylated glycozoline (**148**) which was found active against *Trychophyton rubrum*. Subsequently Nakamura *et al.* discovered antibiotic alkaloid from *Streptoverticilum ehminse* which gave the alkaloids the true status of antibiotics. The most active alkaloid is carbazomycine B which is active against Trycophyton species. There has been widespread interest in the area of the biological properties of carbazole alkaloids and congeners after our report[7,9] (Table 1).

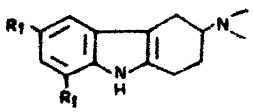


(148)

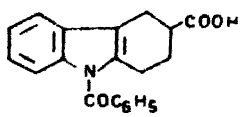
TABLE 1—PROGRESS IN INVESTIGATIONS OF BIOLOGICAL ACTIVITIES OF CARBAZOLES DURING 1965–1988

1965	Antibiotic activities[1]
1977	Antibiotic activity, feeble activity against KB cell culture, some anticancer activity[19]
1983	Antibiotic, anticancer, CNS, antiinflammatory, antifertility and hypercholestermic, trypnocidal, insecticidal[6,8,21] activities
1988	Antibiotic, antiviral, anticancer, CNS, antianxiety, antiemetic and antivomitic activities, control of gastric evacuation, 5HT antagonastic, psychotic disorder, neuroleptic agent, enzyme inhibitory, anabolic activity, diazopam-like activity[22,23], tyrosinase inhibitory activity

The most significant development is the discovery of compounds of drug value[8,2]. Cycloindole (**149**) and flucindole (**150**) are two neuroleptic agents while oxaarbazole (**151**) is antiallergic. The analgesic and antiinflammatory properties of carpofen (**152**) have received widespread attention. Its activities are comparable to those of indomethacin with a greater safety margin.



(148) R_1 = H
(150) R_1 = F



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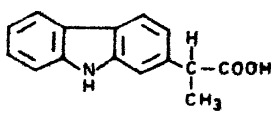

(152)

The stagewise progress of this new group of alkaloids are briefly presented in Table 2.

TABLE 2—PROGRESS IN CARBAZOLE ALKALOIDS

Year	No of alkaloids known	Carbon skeleton	Cyclic system
1962	2[a]	C-13, C-18	Tri-, tetracyclic bases
1971	19[b]	C-13, C-18, C-23	Tri-, tetra-, penta-hexacyclic bases
1977	33[c]	C-13, C-18, C-23	Tri-, tetra-, penta-, hexacyclic bases
1980	37[d]	C-13, C-18, C-23	Tri-, tetra-, penta-, hexacyclic bases
1984	41[e]	C-13, C-18, C-23; C-14, C 19 (from lower plants)	Tri-, tetra-, penta-, hexacyclic bases
1987	65[f]	C-13, C-18, C-23; C-14, C-19 (from lower plants), dimeric C-26, C-36, C-41	Tri-, tetra-, penta-, hexacyclic bases, dimeric C-13+C+13, C-18+C-18, C-18+C-23
1988	80[g]	C-13, C-18, C-23, C-14, C-19 (from lower plants); dimeric C-31	Tri-, tetra-, penta-cyclic bases, dimeric C_{18}+C-18

[a]Ref.: Author, unpublished in 1962. [b]Ref. 79. [c]Ref. 18. [d]Ref. 31. [e]Ref. 63. [f]Ref. 32. [g]Ref. 81.

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