Tetrahedron Letters No. 46, pp 4387 - 4390, 1971. Pergamon Press. Printed in Great Britain.

A GENERAL THREE-STEP SYNTHESIS OF PYRROLIDINO[2,1-b]QUINAZOLONE ALKALOIDS VIA BIOGENETICALLY PATTERNED PATH[*1]

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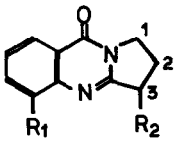
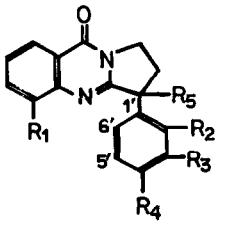
(Received in Japan 8 October 1971; received in UK for publication 12 October 1971)

In 1967, Arndt, Eggers, and Jordaan[1] isolated several minor alkaloids in addition to vasicine from Anisotes sessiliflorus (Acantaceae), and they clarified that these alkaloids had closely related structures (Ib, Ic, IIa-IIc) consisting of substituted pyrrolidinoquinazolone ring system. An alkaloid (IId) in this class has recently been added by the investigation of Johne, Gröger, and Hesse.[2]

Ia-j



IIa-f



	R_1	R_2	alkaloid
Ia	H	OH	vasicinone
Ib	H	EtOOC-NH-	anisessine
Ic	OMe	-NMePh	"sessiflorine"
Id	H	H	deoxyvasicinone

	R_1	R_2	R_3	R_4	R_5	alkaloid
IIa	H	H	COOMe	NHMe	H	anisotine
IIb	OMe	NMe	H	H	H	deoxyaniflorine
IIc	OMe	NMe	H	H	OH	aniflorine
IId	H	NMe	H	H	H	vasicolinone
IIe	OMe	H	H	NHMe	H	sessiflorine
IIf	OMe	NHMe	H	H	H	---

We now report a simple and versatile synthetic method of these alkaloids, which involves the successful syntheses of vasicinone (Ia), anisessine (Ib), and "sessiflorine" (Ic), particularly claming that the structure (Ic) formerly given to sessiflorine[1] should be revised to IIe.

Assuming that these alkaloids originate from anthranilic acid and γ-amino-butyric acid and that the substituent at C-3 position can rationally be introduced by an oxidative free radical coupling, we are able to postulate the biogenetic path of these alkaloids as is shown in Chart I.[*2]

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*1 Presented in part at the 13th Symposium on the Chemistry of Natural Products (Japan), Sapporo, September 25, 1969. Symposium Papers, p. 75.

*2 There remains the possibility, of course, that this class of alkaloids has originated from the corresponding quinazoline-type of alkaloids. In any case, such consideration provides only an indirect route for the synthesis of quinazolone-type alkaloids.

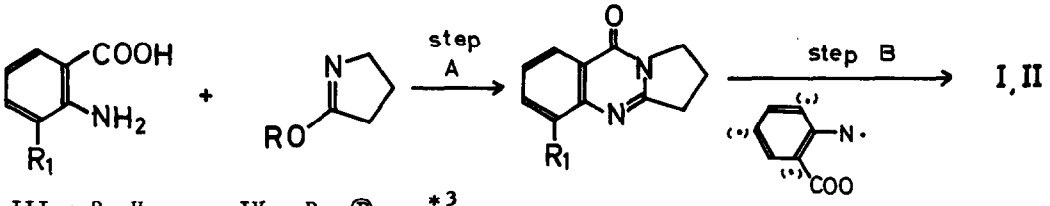
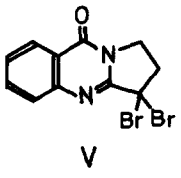


Chart I

In the actual synthesis, we chose the stable but sufficiently reactive O-methylbutyrolactim[3] (IVb) as the laboratory variant of the assumed biological intermediate (IVa) with the anticipation of tracing the naturally occurring condensation process (step A in Chart I). The proposed condensation of IIIa with IVb has been studied by Petersen and Tietze in 1959.[4]

When anthranilic acid (IIIa) or 3-hydroxyanthranilic acid (IIIb) was refluxed with a slight excess of O-methylbutyrolactim (IVb) in benzene solution, the respective pyrrolidinoquinazolone, Id[5] or Ie, was formed in the yield as high as 82%.

The second stage of the synthesis is the introduction of an easily convertible functional group to C-3 carbon atom in analogy with the assumed biological coupling process B in Chart I. Considering that the process B must be achieved in plant by free radical oxidation reaction, we adopted a free radical bromination with NBS for the laboratory simulation of this process. NBS bromination of Id in CCl_4 solution in the presence of benzoyl peroxide afforded the desired monobromide If in a 57% yield, which was accompanied by a small amount of a dibromide (V). A similar reaction of Ii, derived from Ie with diazomethane, furnished Ij in the same yield. While the position of brominated site might be assumed as C-3 from NMR data (see Table I), this was further proved by the conversion of If to vasicinone (Ia).



V

	C(1)H	C(2)H	C(3)H
Id	4.18	3.17	3.15
Ie	4.34	2.27	3.14
Ii	4.22	2.28	3.07
If	4.32	~2.7	5.25
Ij	~4.3	2.7	5.38
V	4.24	3.30	-
Ig	4.18	~2.6	6.07

Table I NMR data in $CDCl_3$ (δ)

	R_1	R_2	mp (°C)
Ic	OMe	-NMePh	199-200
Ie	OH	H	158-160
If	H	Br	147-149
Ig	H	OAc	133-134.5
Ih	H	-NMePh	162-163.5
Ii	OMe	H	157-159
Ij	OMe	Br	160-162

Table II

*3 There is no distinct evidence for the existence of such Vilsmeier-type intermediate in the alkaloid biosynthesis, but it would be interesting to speculate that these amide phosphates (and/or pyrophosphates) and carbinol amine phosphates take an important part as an active intermediate in the biological system.

Treatment of the bromide If with AcONa-AcOH gave acetylvasicinone (Ig) in 33% yield, which was also derived from the mother compound Id by a free radical oxidation with $Pb(OAc)_4$-benzene in a low yield (4%).[6] Acetylvasicinone (Ig) was then converted to dl-vasicinone (Ia) which was identified by mixed mp determination and IR spectral comperison with the authentic specimen[7] prepared from natural dl-vasicine. This conversion provides not only the chemical proof for the presence of a bromine atom at C-3, but also an effective route to vasicinone, known as a minor alkaloid[5,7] with bronchdilating action,[8] starting from anthranilic acid in an overall yield of 17%.

Nucleophilic replacement of bromine atom with a suitable aromatic amine, required for the completion of the synthesis of Anisotes alkaloids, was effected by simply mixing the bromide (If or Ij) with an appropriate amine (ethyl anthranilate or monomethylaniline) and warming the mixture at about 70°. Purification through preparative TLC furnished the desired product (Ib, Ic or Ih) in ca. 20-30% yield. The synthesized anisessine (Ib) thus obtained was completely identical in UV, IR(KBr), MS and NMR spectra, as well as in thin-layer chromatographic behavior and mixed mp determination, with natural dl-anisessine. On the other hand, the compound Ic showed a distinct difference in the thin-layer chromatographic behavior and in spectrometric properties from those of natural sessiflorine, although it should possess the structure given for sessiflorine by the African authors.[1] The comparison of spectral data between Ic and natural sessiflorine (Table III) clearly indicates that the previously assigned structure of sessiflorine (Ic) is not correct and that it should be revised to either IIe or IIf. The proof of the above conclusion is the presence of NH streching vibration ($\nu_{NH}^{CHCl_3}$ 3290 cm^{-1}) in the IR spectrum of sessiflorine, which definitely excludes the structure Ic for natural sessiflorine. In NMR spectrum of natural sessiflorine, C-3 methine proton appears at a higher field (δ 4.66) than the methine proton of C-3 bearing nitrogen (e.g. δ 5.03 for anisessine (Ib); δ 5.47 for Ic), which in turn corresponds to the chemical shift of methine proton of C-3 bearing aryl-substituent (e.g., δ 4.95 for deoxyaniflorine (IIb); δ 4.50 for vasicolinone (IId)). A similar difference between aryl and nitrogen substitution at C-3 is observed in the mass spectra. Sessiflorine shows a parent peak as the base peak analogous to deoxyaniflorine (IIb) and vasicolinone (IId), an alkaloid of the type with C-3 aryl substitution, whereas the synthesized compound exhibits the base peak of M-105(PhNHMe) which is consistent with the C-3 nitrogen-substituted formulation Ic.

	IR	NMR (δ in $CDCl_3$)		
		C(1)$\underline{H}_2$	C(3)$\underline{H}$	#
Synthesized Ic	no NH	4.5-3.7(m)	5.47(t,J=8.2)	7.0-6.7(3H,m)
Natural sessiflorine	$\nu_{NH}^{CHCl_3}$ 3290	4.5-4.15(m)	4.66(t,J=6.0)	7.0-6.7(2H,br.d)

Protons ortho and para to nitrogen of the appendant N-methylaniline.

Table III

Of the two revised formulations (IIe or IIf) of sessiflorine, IIe should reasonably be preferred from the shape of NMR signals at δ 7.0-6.7 (2 protons), which appear as A_2 part of A_2B_2 type of spectrum and is attributable to 3' and 5' hydrogens of appendant methylaniline moiety. Another proof of the preference of structure IIe is that N-methyl protons resonate at δ 2.95 in concordance with that of anisotine (IIa, δ 2.88), whereas the ortho-substituted isomers show the N-methyl signals at a higher field owing to the shielding effect of quinazolone ring (e.g. δ 2.59 for deoxyaniflorine (IIb) and δ 2.67 for vasicolinone (IId)). On these grounds, we propose the structure IIe as the correct formulation for natural sessiflorine which hitherto had been incorrectly expressed by Ic.[1)]

Acknowledgment

The author expresses his deep gratitude to Dr. M. Natsume, Director of this Laboratory, for his never-failing guidance throughout this work. The author takes this opportunity to express his hearty thanks to Professor Emeritus E. Ochiai of the University of Tokyo for his interest and encouragement. Grateful thanks are due to Dr. S. H. Eggers of Pretoria for providing the valuable samples of natural vasicine, anisessine and sessiflorine and also their spectroscopic data. This work was supported by Grant-in-Aid of Ministry of Education, which is gratefully acknowledged.

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