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"HOMO-*PICTET-SPENGLER* " CYCLIZATION OF TRYPTAMINES: AN EASY ACCESS TO THE HEXAHYDROAZEPINO[4,5-b]INDOLE RING SYSTEM.

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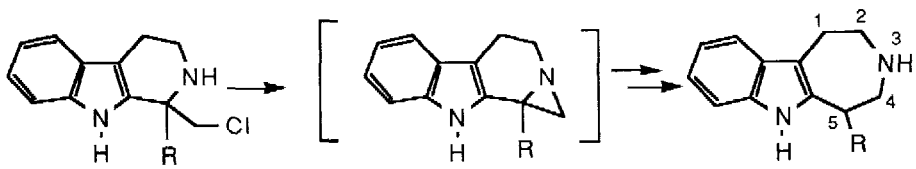
Summary: The title compounds were prepared in one step from tryptamines **3** and α-bromoaldehydes **4**.

Synthesis of the hexahydroazepino[4,5-b]indole system through ring expansion of a tetrahydro-ß-carboline has been little studied until now: the model compound **2a** (Scheme 1) was prepared by Julia[1] from 1-chloromethyl-ß-carboline **1a** via the intermediate aziridine. Later, Kuehne obtained compound **1b** through the Pictet-Spengler cyclization of tryptamine with methyl chloropyruvate and further rearranged it to his highly potent azepinoindolic synthon **2b**[2].



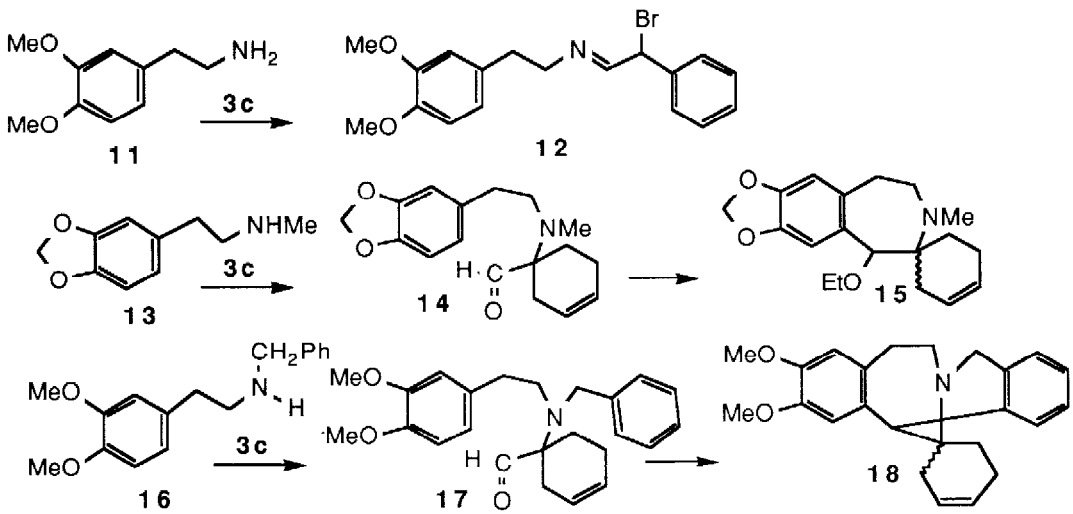
1a R = H
1b R = COOMe

2a R = H
2b R = COOMe

Scheme 1

We have now studied the reaction of tryptamines with some α-bromoaldehydes[3] along similar lines, in order to prepare 4,4-disubstituted hexahydroazepino[4,5-b] indoles (Scheme 3, Table). We found that heating tryptamine **3a** with α-bromo aldehydes **4a-d** in acetic acid at 70°C for 15 hrs afforded in one step the 5-acetoxy-4,4-dialkylhexahydroazepinoindoles **5a-d** in yields ranging from 34 to 75% With 5-methoxytryptamine **3b** and bromoaldehydes **4a** or **4c** the synthesis of **5e** and **5f**, respectively, was completed within only 2 hrs. On the contrary, reaction of *N(b)-methyl* tryptamine **3c** with bromoaldehyde **4c** was very sluggish: compound **5g** was isolated (42%) after a 100 hr heating in AcOH, together with aldehyde **10** (X = H, R_1, R_2 = $-CH_2-CH=CH-CH_2-CH_2-$; R_3 = Me) (11%) and methyltryptamine. When the reaction was stopped after 6 hrs, aldehyde **10** was isolated (36%) as the sole reaction product. Compound **10** could further be cyclized in AcOH to **5g**.

With N(b)-unsubstituted tryptamines (R_3 = H) the initially formed carbinolamine **6** gives iminium **7** which leads to aziridinium **8** along (concerted?) Pictet-Spengler cyclization and bromine elimination. Finally, attack by an acetate gives the 5-acetoxyhexahydroazepinoindoles **5a-f**. Electron enrichment of the indole nucleus by a methoxy group (X=OMe) accelerates the Pictet-Spengler cyclization. No diastereoselection was observed in the formation of **5c-d** and **5f-g** with regard to the poor discrimination between R_1 and R_2. With the N(b)-substituted tryptamine (R_3 = Me) carbinolamine **6** rearranges to aldehyde **10**[6] *via* aziridinium **9.** Further cyclization of **10** to **5g** is precedented[7].



Scheme 2

Intermediacy of **7** or **10** (depending on the substitution of N(b) in tryptamines) was substantiated by the reactions of some α–bromoaldehydes with phenethylamine derivatives (scheme 2). In no case was the one-step cyclization in AcOH observed. Heating homoveratrylamine **11** and bromoaldehyde **3c** in AcOH yielded bromoimine **12** which could not be further cyclized. Treatment of N-methylhomopiperonylamine **13** with **3c** and K_2CO_3 in refluxing DME for 4 days gave aldehyde **14** (48 %), which was cyclized to benzazepine **15** (24%) upon reaction with TFAA and BF_3 etherate (probably through an acylal intermediate[8]) A similar sequence starting from N-benzylhomoveratrylamine **16** and **3c** gave aldehyde **17** (51%) whose cyclization (BF_3 etherate) was accompanied with a supplementary ring closure affecting the benzene ring, which yielded compound **18** (66%) along a not uncommon reaction pathway[9,10]

The use of α–bromoaldehydes in such "homo-Pictet-Spengler" cyclizations then appears of interest in the synthesis of fused azepino- ring systems Further applications in the azepinoindole series are under current study

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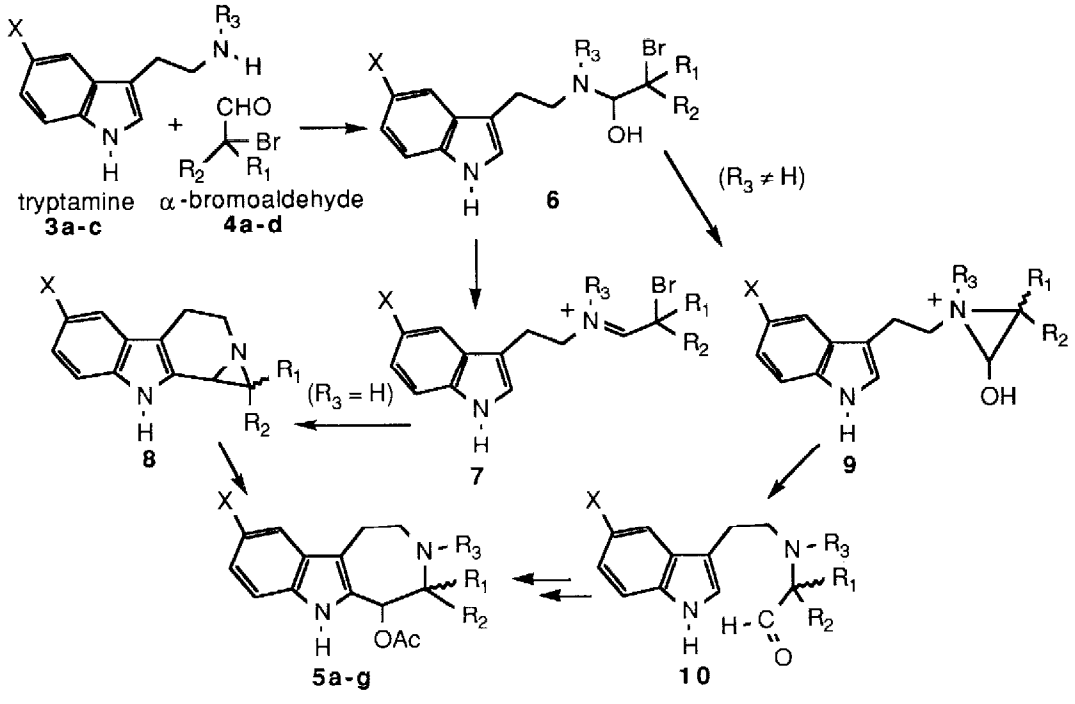

Scheme 3

tryptamine			α-bromoaldehyde			time of reaction	product (yield %)
	X	R_3		R_1	R_2		
3a	H	H	**4a**	Me	Me	15 hrs	**5a** (34)
3a	H	H	**4b**	Et	Et	15 hrs	**5b** (56)
3a	H	H	**4c**	$-CH_2-CH=CH-CH_2-CH_2-$		15 hrs	**5c**[a](70)
3a	H	H	**4d**[4]	$-CH_2\,CH=C(Me)-CH_2-CH_2-$		15 hrs	**5d**[a](75)
3b	MeO	H	**4a**	Me	Me	2 hrs	**5e** (66)
3b	MeO	H	**4c**	$-CH_2-CH=CH-CH_2-CH_2-$		2 hrs	**5f**[a](72)
3c	H	Me	**4c**	$-CH_2-CH=CH-CH_2-CH_2-$		100 hrs	**5g**[a](42)

[a] mixture of isomers

Table[5]

References and Notes

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3. The starting aldehydes were brominated in nearly quantitative yield by using the $CuBr_2$ bromination method developed for ketones by Brown: Brown, E. C.; Rogié, M. M ; Rathke, M. M. *J. Amer. Chem. Soc.* **1968**, *90*, 6218
4 1-methyl-4-bromo-4-formylcyclohexene **4d** was prepared by Diels-Alder cyclization of isoprene with 2-bromoacrolein.
5 All new products were fully characterized by their UV, IR, mass, ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra. Most salient features for compounds **5a-g** were an easy loss of AcOH from the molecular ion in the mass spectra (M-60) and a low field proton at ~ 5.7 ppm (H-5) in the ^1H NMR spectra C-4 and C-5 were seen at 42-44 and 72-75 ppm, respectively, in the ^{13}C NMR spectra.
6 Reaction of α-halogenocarbonyl compounds with secondary amines is known to yield α-aminocarbonyl derivatives: De Kimpe, N.; Verhe, R. *The Chemistry of α–haloketones, α–haloaldehydes and α–haloimines* J Wiley, Ed , New-York, **1988**.
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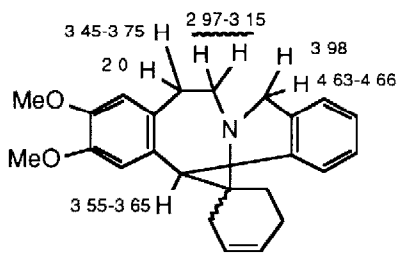
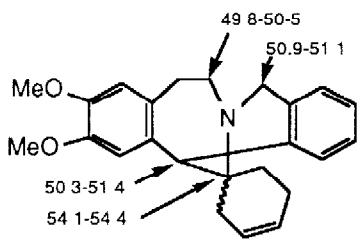
9 Obtained as a mixture of isomers. The following ^1H and ^{13}C data were supported by COSY measurements.





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