77.4; H, 7.6; N, 15.0. Found: C, 77.2; H, 7.9; N, 14.8.

**Equilibration of Indole Nitrile 53.** A solution of **53** (732 mg) in TFA (5 mL) was refluxed for 24 h, diluted with saturated $NaHCO_3$ (100 mL), and extracted with $CH_2Cl_2$ (3 × 20 mL). The $CH_2Cl_2$ extracts were dried and evaporated, and the residue was chromatographed (disk, 2 mm, 30 to 50% EtOAc in isooctane) to give 325 mg (44%) of educt **53**, followed by 333 mg (46%) of desired indole nitrile 4.

**1-Cyano-1-ethyl-12-[(methoxycarbonyl)methyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (54).** To a solution of 4 (482 mg) in DMF (15 mL) at 0 °C was added NaH (1.5 g, 50% in oil). After it was stirred for 1 h, the mixture was cooled to −30 °C and methyl bromoacetate (3.0 mL) was added. After the solution was stirred for 1 h, the reaction was quenched with MeOH (1 mL), diluted with saturated $NaHCO_3$ (20 mL) and water (50 mL), and extracted with EtOAc (100, 30 mL). The combined organic extracts were extracted with 1 M $H_3PO_4$ (3 × 50 mL), which was basified with $NH_4OH$ (25 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined $CH_2Cl_2$ extracts were dried and evaporated, residual solvent was entrained with toluene (2 × 250, 50 mL), and the residue was chromatographed (disk, 2 mm, 50–100% EtOAc in isooctane) to give 413 mg (71%) of **54**: mp 203–205 °C; $[\alpha]^{20}_D$ −108° (*c* 2, $CHCl_3$); IR (Nujol) 2250, 1765, 45 $cm^{-1}$; $^1H$ NMR δ 7.54 (d, *J* = 7.5 Hz, 1 H), 7.3–7.1 (m, 3 H), 4.81 (d, *J* = 17.8 Hz, 1 H), 4.59 (d, *J* = 17.8 Hz, 1 H), 3.9 (m, 1 H), 3.68 (s, 3 H), 3.62 (s, 1 H), 3.3–1.4 (m, 11 H), 1.03 (t, *J* = 7.3 Hz, 3 H). Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.8; H, 7.2; N, 12.0. Found: C, 71.9; H, 7.2; N, 11.9.

**(3*S*,16*R*)-14-(Methoxycarbonyl)-15-oxoeburnane (55).** To a solution of diisopropylamine (0.1 mL) in THF (1 mL) at 0 °C was added *n*-BuLi (0.3 mL, 1.4 M in hexane). After it was stirred for 15 min, the solution was cooled to −78 °C and nitrile ester **54** (52 mg) was added as a solution in THF (2 mL). The reaction was stirred at −78 °C for 15 min and then at 0 °C for 9 h, diluted with saturated $NaHCO_3$ (10 mL), and extracted with EtOAc (2 × 10 mL). The combined EtOAc phases were extracted with 1 M $H_3PO_4$ (3 × 10 mL); the acid phases were made basic to pH 8 with $KHCO_3$ and then extracted with $CH_2Cl_2$ (3 × 10 mL). Evaporation of the dried $CH_2Cl_2$ extracts and chromatography (disk, 1 mm, 20% isooctane in EtOAc) of the residue gave 29 mg (56%) of **55**: $[\alpha]^{20}_D$ +97° (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 1755, 1720 $cm^{-1}$; $^1H$ NMR δ 7.6 (m, 1 H), 7.3–7.1 (m, 3 H), 5.54 (s, 1 H), 4.59 (s, 1 H), 3.73 (s, 3 H), 3.6–1.2 (m, 12 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

**(3*S*,14*S*,15*S*,16*R*)-14-(Methoxycarbonyl)-15-hydroxyeburnane (56).** To a solution of **55** (29 mg) in MeOH (1 mL) at −25 °C was added $NaBH_4$ (20 mg). After the mixture was stirred for 3 min, the reaction was quenched with AcOH (0.2 mL), diluted with saturated $NaHCO_3$ (10 mL), and extracted with $CH_2Cl_2$ (10, 5 mL). The $CH_2Cl_2$ extracts were dried and evaporated, and the residue was chromatographed (disk, 1 mm, 100/40/10 isooctane/EtOAc/MeOH) to give 26 mg (90%) of **56**, identical ($^1H$ NMR) with that reported previously.[10]

**Apovincamine (5).** To a solution of **56** (20 mg) in $CH_2Cl_2$ (1 mL) at 0 °C was added $Et_3N$ (0.3 mL) and MsCl (0.1 mL). After stirring for 30 min, the solution was diluted with saturated $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (10, 2 × 5 mL). The $CH_2Cl_2$ extracts were dried and evaporated, and the residue was dissolved in DBU (0.2 mL), heated at 100 °C for 1 h, diluted with saturated $NaHCO_3$ (30 mL), and extracted with $CH_2Cl_2$ (3 × 10 mL). The $CH_2Cl_2$ extracts were dried and evaporated, and the residue was chromatographed (disk, 1 mm, 100/40/10, isooctane/EtOAc/MeOH) to give 11 mg (55%) of **5**, identical (IR, $^1H$ NMR) with a sample prepared by acid-catalyzed dehydration of vincamine.[11]

**Optical Purity Determination. Apovincaminic Acid Methyl Mandelate Ester (58).** To a solution of apovincamine (**5**, 48 mg) in MeOH (2.5 mL) and THF (2.5 mL) was added 2 N NaOH (5 mL). After stirring for 12 h, the solution was taken to pH 6 with 1 M $H_3PO_4$ (5 mL), and extracted with 25% *i*-PrOH in $CHCl_3$ (3 × 20 mL). The organic extracts were dried and evaporated to give a crude residue of **57**, which was dissolved in pyridine (5 mL), (±)-methyl mandelate (50 mg) was added, the solution was cooled to 0 °C, and TsCl (200 mg) was added. After it was stirred for 1 h, the solution was diluted with saturated $NaHCO_3$ (50 mL) and $CH_2Cl_2$ (20 mL) and stirred at room temperature for 1 h, the phases were separated, and the aqueous phase was extracted with additional $CH_2Cl_2$ (2 × 20 mL). The combined $CH_2Cl_2$ extracts were evaporated, the residue was dissolved in EtOAc (20 mL) and extracted with 1 M $H_3PO_4$ (40, 2 × 20 mL), and the separate acid extracts were sequentially back extracted with EtOAc (2 × 20 mL). These acid phases were then combined, basified with $NH_4OH$ (20 mL), and extracted with $CH_2Cl_2$ (20, 2 × 10 mL). The final extracts were dried and evaporated to give 57 mg (84%) of ester **58a**: $^1H$ NMR (**58b**, other diastereomer) δ 6.19, 6.45 (s, 1 H), 6.15, 6.16 (s, 1 H), 4.14, 4.17 (s, 1 H), 3.83, 3.77 (s, 3 H), 0.96, 1.05 (t, *J* = 7.4 Hz, 3 H). Anal. Calcd for $C_{29}H_{30}N_2O_4$: C, 74.0; H, 6.4; N, 6.0. Found: C, 74.2; H, 6.6; N, 6.0.

For the determination of optical purity, apovincamine (**5**) was coupled separately to (+)- and (±)-methyl mandelate as above, except that the acid–base extraction was omitted. The optical purity was determined exactly as described for **49**, and was found to be >99%.

# Studies of Rutaecarpine and Related Quinazolinocarboline Alkaloids

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Quinazolinocarboline alkaloids, e.g., rutaecarpine (**1**), can readily be synthesized by treating tryptamine with 2-(trifluoromethyl)-4*H*-3,1-benzoxazin-4-one (quickly generated in situ from trifluoroacetic anhydride (TFAA) and 2*H*-3,1-benzoxazine-2,4(1*H*)-dione. The product formed, 3-[2-(3-indolyl)ethyl]-2-(trifluoromethyl)-4-(3*H*)-quinazolinone (**5**), is then cyclized (HCl/HOAc) to 13b-(trifluoromethyl)-13b,14-dihydrorutaecarpine (**6**), whereupon $CF_3H$ is eliminated by treatment with base. The sequence can conveniently be performed as a three-reaction one-pot procedure giving rutaecarpine (**1**) in 99% yield within 3 h. The approach can readily be extended to the synthesis of evodiamine (**2**), 13,13b-dehydroevodiamine (**38a**), and 13b,14-dihydrorutaecarpine (**21**). Thus treatment of 3-[2-(3-indolyl)ethyl]-4(3*H*)-quinazolinone (**19**) with TFAA effected cyclization to 13b-(trifluoroacetyl)-13b,14-dihydrorutaecarpine (**20**), which can be readily hydrolyzed to 13b,14-dihydrorutaecarpine (**21**).

The dried fruit of *Evodia rutaecarpa* has a long traditional[1] in Chinese medicine and under the name Wu-Chu-Yu the drug has been used against, e.g., headache, dysentery, cholera and worm infestations.[2]

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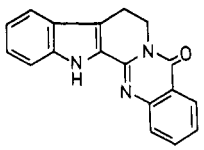
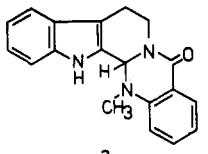
The two main alkaloids, rutaecarpine (1) and evodiamine (2), were first isolated by Asahina[3] around 1915. More than



1



2

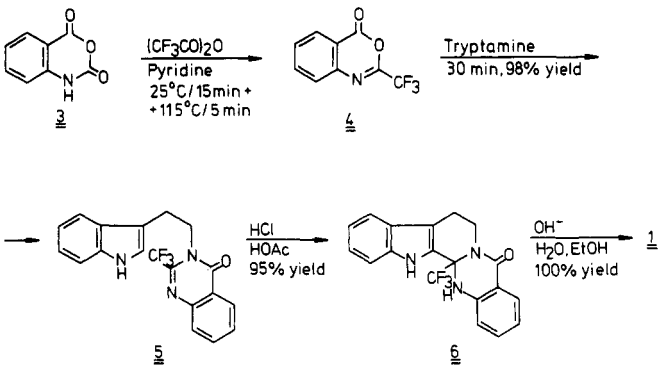
a decade later the first syntheses were reported (rutaecarpine by Asahina, Manske, and Robinson[4] and evodiamine by Asahina and Ohta[5]). Since then several other routes[6a] have been developed. In this paper we will report the details[7] of fast high-yield routes (Schemes I and II) to rutaecarpine, 13b-14-dihydrorutaecarpine, 14-formyl-13b,14-dihydrorutaecarpine, and evodiamine. All those compounds have earlier been isolated[8] from *Evodia rutaecarpa*. Other plants containing quinazolinecarboline alkaloids[6a] include *Hortia arborea*, *Euxylophora paraensis*, *Zanthoxylum rhessa*, and *Vepris louisii*[6b] all members of the Rutacae family.

**Rutaecarpine and Derivatives.** Kametani has recently shown[9] that rutaecarpine can be prepared by reaction of *N*-formyltryptamine with **43** to yield 3-[2-(3-indolyl)ethyl]-4(3*H*)-quinazolinone (**19**), followed by acid treatment for 166 h at 110 °C. Some of the problems involved in this synthesis are the low yield[10,11] of **19** coupled with the necessary chromatography of the multicomponent mixture and the long reaction time and relatively low yield in the final cyclization step. These problems led us to develop the sequence outlined in Scheme 1. In the crucial step (**5** → **6**) in the new procedure (Scheme I), protonation of the 4(3*H*)-quinazolinone moiety of **5** followed by electrophilic attack on the indole ring leads to **6**, a compound with an angular $CF_3$ group in the 13b-position.

In spite of the acidic conditions (HCl/HOAc) compound **6** was isolated as the free base. This low basicity thus demonstrated is in harmony with earlier reports[12] stating that evodiamine (**2**) could not be protonated even by strong acids.

The structure of **6** was based on $^{13}C$ spectroscopy, which showed a quartet at 70.6 ppm ($J_{FC_{13b}}$ = 29.8 Hz)[13] whereas the signal from the $CF_3$ group appeared (as expected) as a quartet around 125 ppm ($J$ = 296 Hz).[14,15] In the mass spectrum of **6** a weak parent ion appeared at $m/z$ = 357. Facile elimination of $CF_3H$ was indicated by the base peak at $m/z$ = 287. In contrast the isomer and precursor,

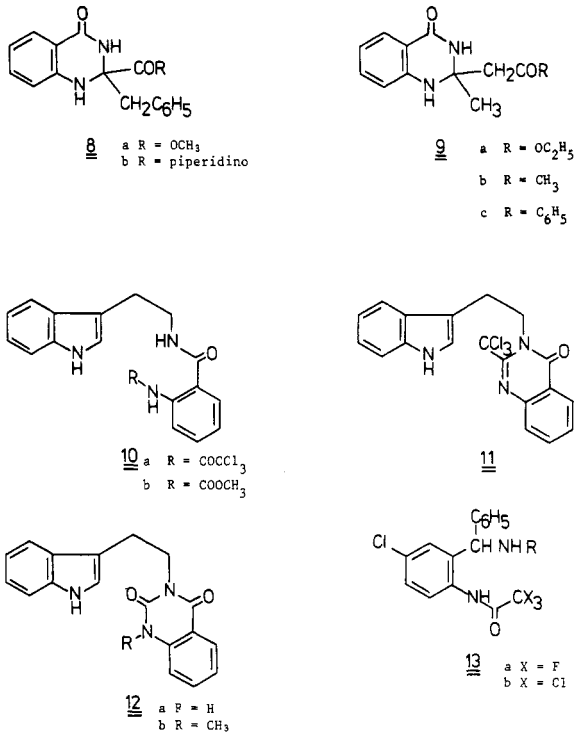
**Scheme I**




compound **5**, exhibited no peaks at all in the region around $m/z$ 287. A weak parent ion peak from **5** appeared at $m/z$ = 357. The main fragments were formed by $\alpha$- and $\beta$-cleavage of the tryptamine unit.

In spite of the facile $CF_3H$ elimination indicated by mass spectrometry it was found that **6** is thermally rather stable although sublimation at 240 °C under reduced pressure resulted in elimination of $CF_3H$ and formation of rutaecarpine (**1**) in high purity.

Related eliminations of quinazolin-4(3*H*)-ones have been reported by Rhee and White[16] who found that the 1,2-dihydroquinazolin-4(3*H*)-one (**8a**) underwent, in refluxing




xylene, a remarkably facile elimination of $C_6H_5CH_3$ to furnish 2-carbomethoxy-4(3*H*)-quinazolinone. On the other hand treatment of the piperidide (**8b**) in refluxing

(1) Li, S. C. "Pentsau Kang Mu"; 1596; Chapter 32.
(2) Chen, A. L.; Chen, K. K. *J. Am. Pharm. Assoc.* **1933**, *22*, 716.
(3) Asahina, Y. *Acta Phytochim.* **1922**, *1*, 67.
(4) Asahina, Y.; Manske, R. H. F.; Robinson, R. *J. Chem. Soc.* **1927**, 1708.
(5) Asahina, Y.; Ohta, T. *Ber.* **1928**, *61*, 319.
(6) (a) Bergman, J. In "The Alkaloids"; Brossi, A. R., Ed.; Academic Press: New York, 1983; Vol. 21, p 29. (b) Ayafor, J. F.; Sondengam, B. L.; Ngadjui, B. T. *Phytochemistry* **1982**, *21*, 2733.
(7) (a) A preliminary report[7b] is available. (b) Bergman, J.; Bergman, S. *Heterocycles* **1981**, *16*, 347.
(8) Kamikado, T.; Murakoshi, S.; Tamura, S. *Agric. Biol. Chem.* **1978**, *42*, 1515.
(9) (a) Kametani, T.; Van Loc, C.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306. (b) Kametani, T.; Ohsawa, T.; Ihara, M.; Fukumoto, K. *Chem. Pharm. Bull.* **1978**, *26*, 1922.
(10) In our hands the yield of rutaecarpine using this procedure never exceeded 10%.
(11) In this connection it should be noted that rutaecarpine can also be prepared[11b] from 3,4-dihydro-$\beta$-carboline[11c] and the sulfinamide anhydride available from $SOCl_2$ and anthranilic acid. (b) (Kametani, T.; Higa, T.; Van Loc, C.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186. (c) A compound that is not easy to prepare.[11d] (c) Szantay, Cs.; Töke, L.; Barczai, M. B.; Kalaus, Gy. *Period. Polytech. Chem. Eng.* **1965**, *9*, 231.
(12) Asahina, Y.; Ohta, T. *Ber.* **1928**, *61*, 319 and papers cited therein.
(13) (a) This value might be compared with that reported[13b] (66.67 ppm) for C-2 in 2-methyl-1,2-dihydro-4(3*H*)-quinazolinone as well as with that reported[13c] (67.9 ppm) for C-13b in 7-carbomethoxyevodiamine. (b) Bergman, J.; Eklund, N. *Chem. Scripta* **1982**, *19*, 193. (c) Danieli, B.; Palmisano, G. *J. Chem. Soc., Chem. Commun.* **1982**, 1092.
(14) In order to make complete assignments a few model compounds, such as 2-(trifluoromethyl)-4(3*H*)-quinazolinone, were also studied. For further details see the $^{13}C$ NMR data chart.
(15) (a) These coupling constants are in good agreement with literature data.[15b] (b) Verboom, W.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1982**, *47*, 3339.
(16) Rhee, R. P.; White, J. D. *J. Org. Chem.* **1977**, *42*, 3650.

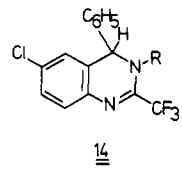
acetic acid yielded[16] the alkaloid glycosminine (2-benzyl-4(3*H*)-quinazolinone).

Elimination at low temperature (KOH in hot EtOH/$H_2O$) of **6** can, as indicated in Scheme I, be induced by base, which also is the preferred synthetic route. In this connection some related base-induced retro-Claisen reactions of **9** leading to 2-methyl-4(3*H*)-quinazolinone are of interest.[17] Eliminations of $CF_3^-$ induced by base have earlier been observed by Kobayashi,[18] who found that 2-(trifluoromethyl)pyridine on treatment with sodium amide was converted into 2-aminopyridine. 2-(Trifluoromethyl)quinoline reacted similarly (for further examples, see ref 19).

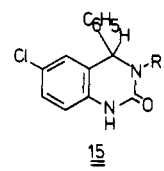
Attempts to effect a noncyclizative variant of the conversion (**5** → **6**) by treating a mixture of 3-methyl-2-(trifluoromethyl)-4(3*H*)-quinazolinone and 3-methylindole with hot HCl/HOAc gave the known dimer of 3-methylindole rather than an adduct. A similar experiment with 2-methylindole, which is known not to oligomerize under the given conditions and also has a reactive site (the 3-position) for electrophilic attack, likewise failed to produce an adduct. Thus juxtaposition of the reacting moieties seems essential for effecting the desired electrophilic attack.

A minor modification of Scheme I would be to start with 2-(trichloromethyl)-4*H*-3,1-benzoxazin-4-one rather than **4**. However, this route proved to be cumbersome. In the first step (reaction of tryptamine with 2-(trichloromethyl)-4*H*-3,1-benzoxazin-4-one) no cyclization occurred and compound **10a** rather than the expected (in analogy with the $CF_3$ case) compound **11** was obtained. Reaction under more vigorous conditions (175 °C) resulted in the formation of a mixture of **11** (minor) and **12a** (major) and unidentified byproducts. Compound **10a** (as well as **10b**) could be readily cyclized to **12a** at low temperature (60 °C) under alkaline conditions. This behavior is in harmony with results earlier reported by Yamamoto,[21,22] who found that **13a** on heating in dioxane preferentially yielded compound **14**, whereas **13b** yielded compound **15**. In this connection it might be added that the activation energy for decarboxylation of trichloroacetic acid is lower than that of trifluoroacetic acid.[23]

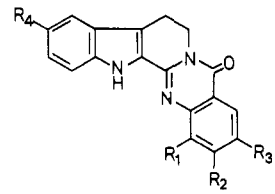
**Euxylophoricine A, Euxylophoricine C, and Related Compounds.** Other quinazolinocarboline alkaloids related to rutaecarpine, such as hortiacine (**16a**) and euxylophoricine C (**17**) could also readily be synthesized by the route in Scheme I. A few purely synthetic analogues (viz., 3-chloro- and 1,3-dichlororutaecarpine) were also prepared. The yields were very high, for example 3-chlororutaecarpine (**16e**) was obtained in 99.5% yield from tryptamine and 6-chloro-2*H*-3,1-benzoxazine-2,4(1*H*)-dione in a three-reaction one-pot sequence using the principles outlined in Scheme I. In this connection it was also found that the appropriate halogenated *N*-trifluoroacetylated anthranilic acids could readily be converted into derivatives of compound **4**, e.g., 6,8-dichloro-2-(trifluoromethyl)-4*H*-3,1-benzoxazin-4-one (**44c**). In some cases it was beneficial to add a cosolvent such as dioxane of DMF to obtain a homogeneous medium in the last step. The crucial step could be followed conveniently by the appearance of a quartet around 70 ppm in the $^{13}C$ NMR spectrum. For the synthesis of euxylophoricine A (**16b**) it was observed that a somewhat longer reaction time (1 h) was necessary in the first step. It is reasonable to assume that the methoxy groups will not only render the carbonyl function less potent in the 6,7-dimethoxy-2-(trifluoromethyl)benzoxazin-4-one (**44a**) but will also increase the basicity of the 14-nitrogen in the 2,3-dimethoxy derivative of **6**. Thus it is not surprising that the product of the reaction is a mixture of the 14-*N*-acetylated compound **22b** (minor) and **22a** (major). For synthetic purpose the involuntary introduction of the acetyl group is immaterial as it is readily removed in the final hydrolysis step. It was also found that **22a** could be obtained faster and more conveniently by performing the reaction in dioxane or sulfolane containing HCl. Similar observations were made in the synthesis of euxylophoricine D (**16c**).



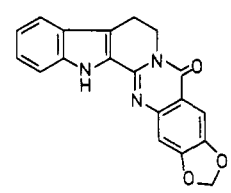
**14**



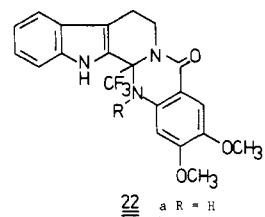
**15**



**16** a $R_2 = R_3 = H$; $R_4 = OCH_3$ b $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$ c $R_1 = H$; $R_2 = R_3 = R_4 = OCH_3$ d $R_2 = R_4 = H$; $R_1 = R_3 = Cl$ e $R_1 = R_2 = R_4 = H$; $R_3 = Cl$



**17**



**22** a R = H b R = $COCH_3$

**13b,14-Dihydrorutaecarpines.** 13b,14-Dihydrorutaecarpine could be readily synthesized as portrayed in Scheme II. The starting material **18**, from isatoic anhydride (**3**) and tryptamine, was reacted with refluxing triethyl orthoformate to yield **19** together with **23** and **24a** as a thick oil, which on crystallization from ethanol/water containing sodium hydroxide (to hydrolyze **23** and **24a**) gave **19** in high yield. Alternatively, **19** could be prepared by heating **18** in formic acid (to yield **24a**) followed by alkaline hydrolysis in aqueous ethanol.

Slow addition of trifluoroacetic anhydride (TFAA) at +2 °C to a well-stirred mixture of **19** in $CH_3CN$ resulted in quick dissolution followed by crystallization of the desired cyclized product **20**. Excess of TFAA and higher temperatures reduced the yield due to competitive *N*-trifluoroacetylation of the indole ring. As before, cyclized and uncyclized products could be disinguished readily by

(17) (a) Manhas, M. S.; Amin, S. G.; Rao, V. V. *Synthesis* **1977**, 309. (b) Mayer, C.; Kappe, Th. *Z. Naturforsch.* **1977**, 32B, 1214.
(18) Kobayashi, Y.; Kumadaki, I.; Taguchi, S.; Hanzawa, Y. *Chem. Pharm. Bull.* **1972**, *20*, 1047.
(19) Burger, K.; Ottlinger, R.; Goth, H.; Firl, J. *Chem. Ber.* **1982**, *115*; 2494.
(20) This compound seems to be semicommercially available (see Technical Bulletin 152 from the Sherwin-Williams Co., Cleveland, OH).
(21) Yamamoto, M.; Yamamoto, H. *Chem. Pharm. Bull.* **1981**, *29*, 2135.
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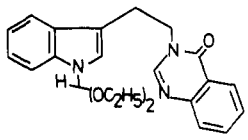
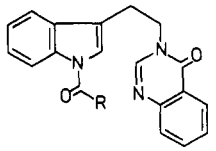
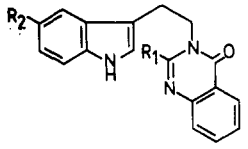
(23) Sayo, H.; Ohmori, H.; Umeda, T.; Masui, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 203.



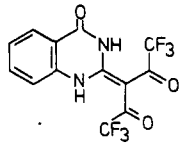
23



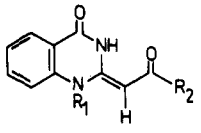
24 a R = H
b R = $CH_3$



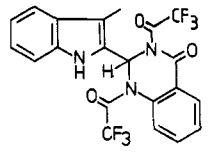
25 a $R_1$ = $CH_3$; $R_2$ = H
b $R_1$ = $C_6H_5$; $R_2$ = H
c R = $CF_3$; $R_2$ = $OCH_3$



26



27 a $R_1$ = $C_6H_5$; $R_2$ = $CH_3$
b $R_1$ = H; $R_2$ = $CF_3$



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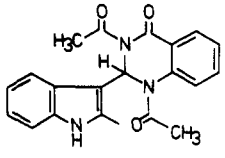
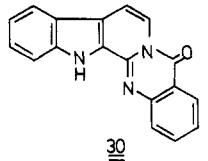


29



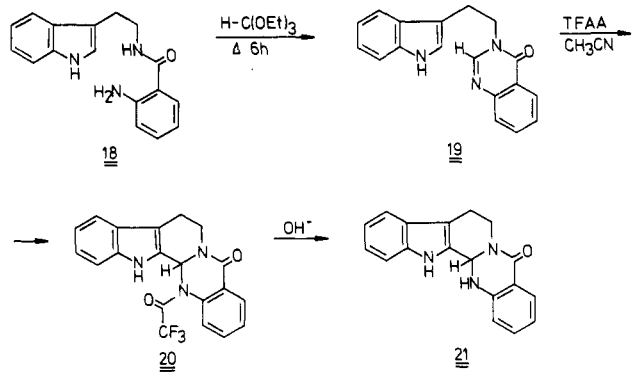
30

the appearance (or nonappearance) of a peak (in this case as a doublet) around 70 ppm in the $^{13}C$ NMR spectrum.

The racemate of the naturally occurring alkaloid[8] 14-formyl-13b,14-dihydrorutaecarpine could similarly be obtained from $HCOOCOCH_3$ and **19**. Under appropriate conditions monoformylation of the NH group in the indole ring (to **24a**) was only a minor by-reaction. On the other hand satisfactory conditions for the conversion of **19** and acetic anhydride into a higher homologue of 14-formyl-13b,14-dihydrorutaecarpine were not found as **24b** was always the predominating product.

To learn more about the cyclization (**19** → **20**) compounds **25a** and **25b**[24] were subjected to the same conditions as **19**. However, $^{13}C$ NMR analysis of the reaction mixtures revealed that no cyclization had occurred. This was confirmed by alkaline hydrolysis of the mixture, which regenerated **25a** and **25b**. The $^{13}C$ NMR analysis of the complex reaction mixture from **25a** also revealed that the $CH_3$ group had been attacked. This was confirmed by a model experiment involving reaction of TFAA with 2-methyl-4(3*H*)-quinazolinone in $CH_3CN$, which yielded compound **26** and also, depending on the conditions, some of **27b**. This facile attack on the 2-methyl group by an acylating agent is not without precedents. Thus heating of 2-methyl-1-phenyl-4(1*H*)-quinazolinone with acetic anhydride has been reported[25] to yield 2-acetonylidene-1-phenyl-4(1*H*)-quinazolinone (**27a**).

**Scheme II**




18 19 20 21

Some other model studies involving 4(3*H*)-quinazolinones are also of interest in connection with the cyclization (**19** → **20**). Thus reaction of 3-methylindole with 4(3*H*)-quinazolinone and TFAA in $CH_3CN$ yielded 3-methyl-2-(trifluoroacetyl)indole rather than an adduct, such as **28**. 2-Methylindole similarly yielded 2-methyl-3-(trifluoroacetyl)indole. It might be added that with acetic anhydride rather than trifluoroacetic anhydride the adduct **29** was obtained in good yield (cf. ref 26).

Compound **19** can be used as a precursor via oxidative couplings to rutaecarpine (**1**) involving reagents such as $Hg(OAc)_2$, $FeCl_3$, and $Pb(OAc)_4$. The reactions are, however, not unexpectedly, rather indiscriminate and complex reaction mixtures were obtained. Only rutaecarpine and dehydrorutaecarpine (**30**) were identified among the array of products. In this connection it was found that 2,3-dichloro-4,5-dicyanoquinone (DDQ) in dioxane readily converted **1** into **30**.[27] Finally it might be added that the interaction of **19** with $Hg(OAc)_2$ was studied already by Clauder,[28] who, however, had erroneously assigned to **19** structure **21**.

**Evodiamine and Related Compounds.** Methylation of **19** with dimethyl sulfate in hot dioxane gave in quantitative yield the methosulfate **31a**, which on treatment with $OH^-$ in water readily gave "isoevodiamine", a compound first described[12] by Asahina. $^{13}C$ NMR data did now show that isoevodiamine has the ring-opened formanilide structure **33a** (cf. ref 27) rather than the cyclized structure (pseudobase) **32a** (in earlier papers the isomeric pseudobase structure **34** has been suggested). The formanilide **33a** could also be prepared readily by treating **33c** (obtained from tryptamine and *N*-methylisatoic anhydride) with $HCOOCOCH_3$ at 25 °C.

The pseudobase is, however, a likely[29] intermediate in the conversion (**31a** → **33a**). It might be added that Tee[30] recently has obtained ample evidence for the involvement of a pseudobase in the base-induced ring opening of 3,4-dihydro-1,3-dimethyl-4-oxoquinazolinium iodide to *o*-(formylmethylamino)-*N*-methylbenzamide. Reduction ($NaBH_4$/MeOH) of **31a** gave quite expectedly the known[27] base **32b**.

Heating of the methosulfate **31a** in the presence of sodium acetate in acetic anhydride was found to be a con-

(24) (a) These compounds were readily obtained by heating (190 °C, 1 h) tryptamine with the corresponding 4*H*-3,1-benzoxazin-4-one. It might be added that tryptamine and unsubstituted 4*H*-3,1-benzoxazin-4-one similarly yielded compound **19**. This procedure to **19** is, however, inferior to the route **18** → **19**, because it is rather time consuming to obtain pure 4*H*-3,1-benzoxazin-4-one.[14b,24c] (b) Zentmayer, D. T.; Wagner, E. C. *J. Org. Chem.* **1949**, *14*, 967. (c) Meth-Cohn, O.; Suschitzky, H.; Sutton, M. E. *J. Chem. Soc. C* **1968**, 1722.

(25) Blatter, H. M.; Lukaszewski, H.; deStevens, G. *J. Org. Chem.* **1965**, *30*, 1020.

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(27) Danieli, B.; Palmisano, G. *Gazz. Chim. Ital.* **1975**, *105*, 99.

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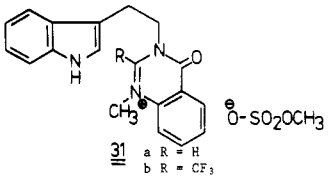
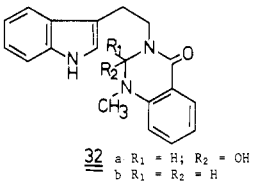
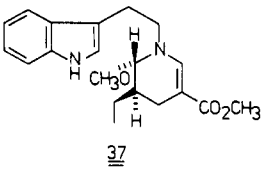
(30) Tee, O. S.; Trani, M.; McClelland, R. A.; Seaman, N. E. *J. Am. Chem. Soc.* **1982**, *104*, 7219.



31 a R = H
b R = $CF_3$



32 a $R_1$ = H; $R_2$ = OH
b $R_1$ = $R_2$ = H



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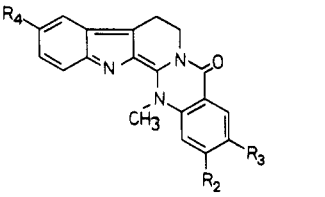
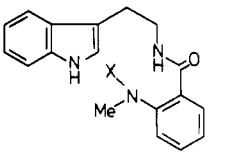
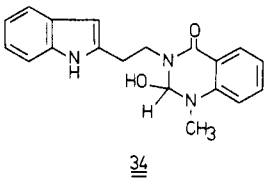


38 a $R_2$ = $R_3$ = $R_4$ = H
b $R_2$ = $R_3$ = H; $R_4$ = $OCH_3$
c $R_2$ = $R_3$ = $OCH_3$; $R_4$ = H
d $R_2$ = $R_3$ = $R_4$ = $OCH_3$



33 a X = CHO
b X = $COCF_3$
c X = H



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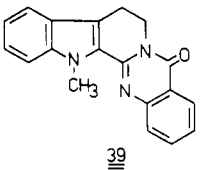

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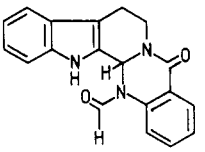

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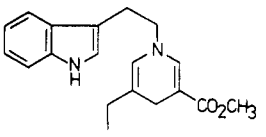

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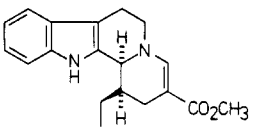

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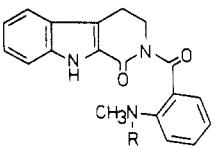
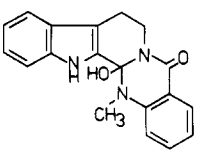


41 a R = H
b R = $CH_3$



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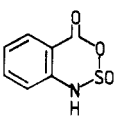

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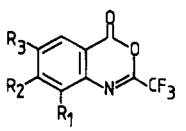

44 a $R_1$ = H; $R_2$ = $R_3$ = $OCH_3$
b $R_1$ = $R_2$ = H; $R_3$ = Cl
c $R_1$ = $R_3$ = Cl; $R_2$ = H

venient route to evodiamine (2), which likewise could be prepared by heating **33a** in acetic anhydride. A similar route to evodiamine (2) has recently been described by Danieli and Palmisano[31] who found that dehydrogenation, induced by $Hg(OAc)_2$, of **32b** readily afforded **2**.

On the other hand, heating of the methosulfate **31a**, even to high temperatures, did not produce any evodiamine. In fact evodiamine and monomethyl sulfate quickly produced (via protonation and ring opening, cf. ref 27) the methosulfate **31a**. The observation that heating of **31a** in the presence of proton-capturing agents (such as $K_2CO_3$) also failed to produce evodiamine is in accordance with the notion that a 5-endo-trig cyclization is disfavored as compared with a 5-exo-tet process (cf. ref 32). In this connection the recently reported[33] stereospecific Pictet–Spengler cyclization (**35** → **36**), which provides strong evidence for an exo-tet process involving **37** is of interest.

**13,13b-Dehydroevodiamine and Related Compounds.** A few 13,13b-dehydro derivatives of evodiamines, such as 13,13b-dehydroevodiamine (**38a**), have been isolated from *Evodia rutaecarpa*, *Hortia arborea*, and a few other plants from the Rutaceae family. Recently Kong[34,35] has reported considerable uterutonic activity[36] of **38a** and hence we became interested in applying the route of Schemes I and II also to this subclass of quinazolinocarboline alkaloids. Compound **38a** was also reported[35b] to lower the blood pressure in rats.

In the first approach **33b** was heated in toluene (100 °C) which resulted (Scheme III) in a cleavage reaction yielding *N*-(trifluoroacetyl)tryptamine (**45**)[43] and the well-known[44] dibenzodiazocine **46**. The desired red-violet alkaloid **38a** was not formed at all. Likewise no elimination of the $CF_3$ group leading to **12b** was observed. Attempts to isolate the assumed intermediate, the pseudobase, failed in spite of the fact that the presence of a $CF_3$ group should invest this pseudobase with increased stability (cf. ref 30). For example, hexafluoroacetone readily forms a stable adduct with water as well as with aniline.[40,41]

Attempts to methylate **5** under the same conditions (dimethyl sulfate in hot dioxane) used for the facile conversion of **19** to **31a** resulted in formation of **6**. No evidence for formation of **31b** was obtained. These results indicate that monomethyl sulfate (formed or present as an impurity in the dimethyl sulfate) was responsible for an acid-catalyzed cyclization (cf. Scheme I) of compound

(31) Danieli, B.; Palmisano, G. *Heterocycles* **1978**, *9*, 803.
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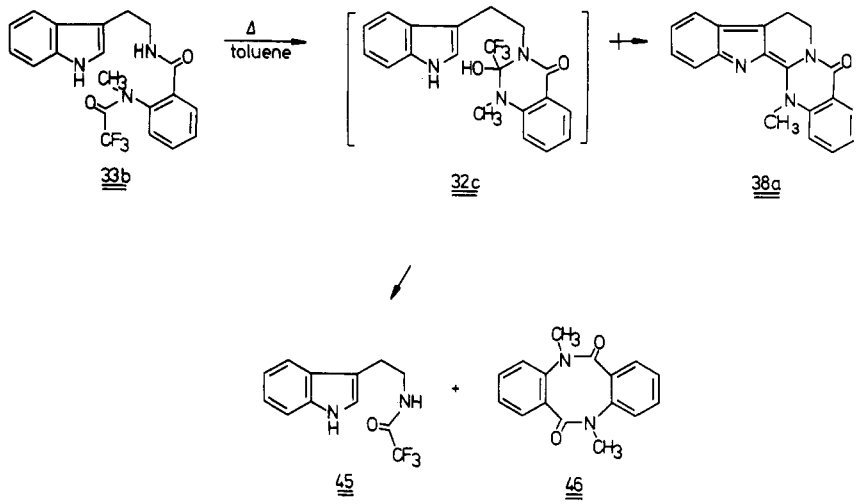
(35) Xu, S. B.; Huang, Y. M.; Lau, C. N. B.; Wat, C. K. H.; Kong, Y. C. *Am. J. Chinese Med.* **1982**, *10*, 75.
(36) Rutaecarpine (1) (as the HCl salt) did also show activity.
(37) Nakasato, T.; Asada, S.; Marui, K. *Yakugaku Zasshi* **1961**, *82*, 619.
(38) Danieli, B.; Palmisani, G. *Gazz. Chim. Ital.* **1975**, *105*, 45.
(39) Danieli, B.; Palmisani, G. *J. Heterocycl. Chem.* **1977**, *14*, 839.
(40) Zeifman, Y. V.; Gamaryan, N. P.; Knunyants, I. L. *Izv. Akad. Nauk. SSSR* **1965**, 450.
(41) Gilbert, E. E.; Jones, E. S.; Sibilia, J. P. *J. Org. Chem.* **1965**, *30*, 1001.
(42) Pachter, I. J.; Raffauf, R. F.; Ullyot, G. E.; Ribeiro, O. *J. Am. Chem. Soc.* **1960**, 82, 5187.
(43) (a) A compound whose GC and MS data are given in the literature,[43b] albeit it has never been isolated before in pure form. An independent synthesis from tryptamine and ethyl trifluoroacetate confirmed the structure. Very recently[43c] *N*-(trifluoroacetyl)tryptamine has been used as starting material in a synthesis of debromoflustramine B. (b) Zeman, A.; Wirotama, I. P. G. *Z. Anal. Chem.* **1969**, *247*, 158. (c) Christophersen, C. In "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, 1983, pp 259, 270.
(44) (a) Cooper, F. C.; Partridge, H. W. *J. Chem. Soc.* **1954**, 3429. Skrob, A. M.; Krülova, J. I.; Antonov, V. K.; Semijakin, M. M. *Zh. Obshch. Khim.* **1969**, *38*, 2051. (c) Bitter, I.; Szöcs, L.; Töke, L. *Acta Chim. Acad. Sci. Hung.* **1981**, *107*, 171.

**Scheme III**



5. Attempts to effect methylation of **5** or **6** under more vigorous conditions (e.g., dimethyl sulfate in hot sulfolane) resulted in the formation of 13-methylrutaecarpine (**39**) rather than **38a**. 13-Methylrutaecarpine had earlier been obtained by methylation[37-39] of rutaecarpine (a likely intermediate in the present case) with methyl iodide at high temperature (120 °C).

At present the best route to **38a** is to heat the readily available compound **33a** in $Ac_2O$, followed by oxidation and dehydration as outlined[37] by Nakasato and Danieli.[31]

13,13b-Dehydroevodiamine (**38a**), as well as hortiamine (**38b**), euxylophorine A (**38c**), and euxylophorine C (**38d**),[42] readily add water[37,45] to yield (in the case of **38a**) the ring-opened β-carboline derivative **41a**. In this conversion the pseudobase **42** is a likely but never isolated or even observed intermediate.[45] In view of the uterutonic[34,35] and hypotensive[35,46] activity reported for **38a** and hortiamine (**38b**) it would be desirable to investigate other derivatives of **38** and also related ring-opened β-carboline derivatives such as **41a** and **41b** to learn whether these compounds are active or not.

**Carbon-13 NMR.** Carbon-13 magnetic resonance spectroscopy is now a well-established[47-50] and powerful tool for structural investigations in the field of indole alkaloids, and throughout this work this technique proved to be of great value. The assignments made (see Chart I) were supported by comparison with literature data as well as information obtained from model compounds. The data given for compounds 1,[51] **49**,[52] and **50**[13b] are taken from the literature. The assignments of the signals from C-11 and C-10 in **1** have been reversed (cf. ref 47a for a similar reassignment of the signals from C-5 and C-6 in indole).

The shift difference observed in the signals from C-2 of **47** and **49** is expected and might be compared with the value for the signals from the carbonyl group in acetic anhydride and trifluoroacetic anhydride, which are 167.3 and 151.5 ppm, respectively.[53] The relatively low value (61.8 ppm) observed from the 13-b carbon atom in compound **40** might be indicative of an interaction of the formyl group with the electron pair on the nitrogen atom in the indole ring.

## Experimental Section

Elemental analyses were performed by Centrala Analyslaboratoriet, Uppsala, Sweden, and all new compounds gave satisfactory (<0.4%) data. All melting points are uncorrected. NMR spectra were recorded on a Bruker WP 200 instrument and a Varian EM-360 instrument (with $Me_2SO$ as solvent, unless otherwise stated and with $Me_4Si$ as internal standard). Infrared spectra (KBr disk unless otherwise stated) were obtained by using a Perkin-Elmer 257 instrument. Mass spectra were obtained with a Varian Mat 311 mass spectrometer (70 eV).

**Isatoic anhydride** (2*H*-3,1-benzoxazin-2,4(1*H*)-dione) of commercial quality (97%, BASF) was generally used without further purification. A material recrystallized from anhydrous pyridine gave usually slightly higher (5–10%) yields.

***N*-Methylisatoic anhydride** was prepared by refluxing *N*-methylanthranilic acid with methyl chloroformate for 7 h. The crystals formed (95% yield) were used directly after washing with $CH_3OH$ and drying.

**Tryptamine and 5-methoxytryptamine** were obtained from Laboratoire Plan, Geneva, Switzerland, or were prepared according to a literature procedure.[54]

**Formic acetic anhydride** was prepared according to Krimen[55] and trifluoroacetic anhydride (TFAA) was obtained from PCR, Gainesville, Fa, or Sigma Chemical Co, St. Louis, MO.

***N*-(2-Aminobenzoyl)tryptamine (18).** A mixture of tryptamine (16.0 g, 0.10 mol) and isatoic anhydride (16.5 g, 0.10 mol) was refluxed (15 min) in ethanol (65 mL). The crystals formed were collected after cooling, yield 26.4 g (94%), mp 160–161 °C (lit.[28] mp 156–157 °C): IR 3403, 3312, 3250 (b), 2908, 1631, 1608, 1588 $cm^{-1}$; MS, *m/z* (relative intensity) 279 (25), 163 (22), 144 (12), 143 (100), 131 (7), 130 (48), 120 (40), 119 (78).

***N*-(2-Aminobenzoyl)-*N*-methyltryptamine (33c).** A mixture of tryptamine (16.0 g, 0.10 mol) and *N*-methylisatoic anhydride (19.9 g, 0.11 mol) was refluxed (1 h) in diglyme (60 mL), whereupon the solution was evaporated and the residue crystallized from toluene (with final cooling to −30 °C), yield 21.3 g (73%), mp 126–127 °C (lit.[12] mp 126 °C).

The analytical sample was recrystallized from benzene: IR 3415, 3313, 3256, 1628, 1578, 1516, 1282, 1170, 749, 738 $cm^{-1}$.

**3-[2-(3-Indolyl)ethyl]-4(3*H*)-quinazolinone (19).** *N*-(2-Aminobenzoyl)tryptamine (**18**, 13.95 g, 0.05 mol) was refluxed

(45) Danieli, B.; Lesma, G.; Palmisano, G. *Heterocycles* **1979**, *12*, 353.
(46) Pachter, I. J.; Mohrbacher, R. J.; Zacharias, D. E. *J. Am. Chem. Soc.* **1961**, *83*, 635.
(47) (a) Gribble, G. W.; Nelson, R. B.; Johnson, J. L; Levy, G. C. *J. Org. Chem.* **1975**, *40*, 3720. (b) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6996.
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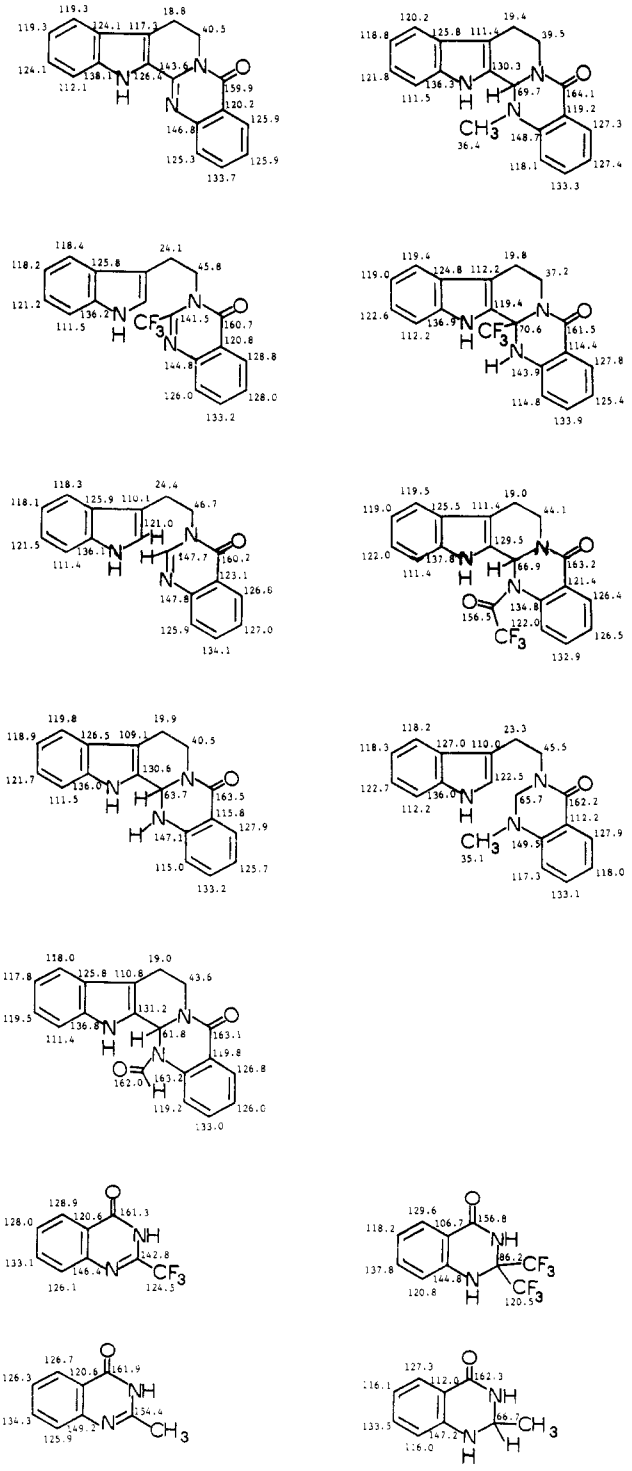
**Chart I**



with triethyl orthoformate (45 mL) for 6 h, whereupon the clear solution was concentrated to a syrup, which was dissolved in and refluxed (30 min) with a solution of the following composition: ethanol (45 mL), water (10 mL), KOH (4.5 g). After cooling and completed crystallization (3 h) the product was collected, washed with ethanol and water, and dried, yield 12.95 g (89%), mp 173–174 °C (lit.[9a] mp 164–165 °C): IR 3375, 1672, 1607, 1470, 1366, 1324, 1151, 773, 736, 698 $cm^{-1}$; MS in agreement with literature data[28] albeit the structure was erroneously reported as **21**; $^1H$ NMR (in agreement with literature data[9a]).

**Chromatographic Separation of a Sample of the Reaction Mixture from 18 and Triethyl Orthoformate.** The syrup (1.0 g) obtained above was chromatographed on silica gel with $CH_2Cl_2$ containing slowly increasing amounts of $CH_3OH$. Three compounds were isolated: **23** (32%), **24a** (18%), and **19** (50%). Compound **23** (an oil) gave the following data: MS, $m/z$ (relative intensity) 391 ($M^+$, 3), 346 (M – $C_2H_5OH$, 6), 317 [(M – ($C_2H_5OH$ + $C_2H_5$)), 8], 244 (3), 172 (12), 171 (100%), only peaks above $m/z$ 170 are listed, the fragmentation pattern below $m/z$ 170 is similar to that of compound **24a**; IR ($CHCl_3$) 1678, 1616, 1522, 1464 $cm^{-1}$.

**3-[2-(*N*-Formyl-3-indolyl)ethyl]-4(3*H*)-quinazolinone (24a). Method A.** *N*-(2-Aminobenzoyl)tryptamine (**18**, 13.95 g, 0.05 mol) was refluxed with formic acid (50 mL) for 4 h, whereupon the clear solution was allowed to cool and then poured with stirring into water (300 mL). The solid formed was recrystallized from dioxane/$H_2O$, yield 13.0 g (82%), mp 233–235 °C: IR 1705, 1672, 1613, 1463, 1393, 1370, 802, 778, 772, 768, 757 $cm^{-1}$; MS, $m/z$ (relative intensity) 317 ($M^+$, 12), 172 (41), 171 (100), 144 (14), 143 (98), 130 (64), 129 (13), 115 (20).

**Method B.** 3-[2-(3-Indolyl)ethyl]-4(3*H*)-quinazolinone (2.89 g, 0.01 mol) was refluxed with formic acid (20 mL) for 3 h, whereupon the solution was concentrated and poured into water. The solid formed was recrystallized from dioxane/$H_2O$, yield 2.60 g (82%), mp 233–235 °C.

**3-[2-(*N*-Acetyl-3-indolyl)ethyl]-4(3*H*)-quinazolinone (24b).** 3-[2-(3-Indolyl)ethyl]-4(3*H*)-quinazolinone (2.89 g, 0.01 mol) was refluxed with acetic anhydride (20 mL) for 3 h. The crystals formed on cooling (finally to –30 °C) were collected, washed with cooled methanol, and dried, yield 2.91 g (88%), mp 190–191 °C: IR 1693, 1669, 1611, 1572, 1557, 1492, 1452, 1438, 1228, 939, 778, 752 $cm^{-1}$.

**Hydrolysis of 24a.** Compound **24a** (3.16 g, 0.01 mol) was refluxed with a solution of the following composition: ethanol (20 mL), water (4 mL), KOH (3.0 g). After cooling and completed crystallization the product was collected, washed with ethanol and water, and dried, to yield 2.54 g (88%), mp 173–174 °C.

This product was identical in all respects with 3-[2-(3-indolyl)ethyl]-4(3*H*)quinazolinone (**19**) as described above. A similar hydrolysis of ccmpound **24b** also reyielded **19**.

**3-[2-(3-Indolyl)ethyl]-2-(trifluoromethyl)-4(3*H*)-quinazolinone (5).** Trifluoroacetic anhydride (7.3 mL, 0.05 mol) was added during 15 min to a well-stirred mixture of isatoic anhydride (8.15 g, 0.05 mol) in pyridine (150 mL) at 25 °C. After completed addition the solution was finally refluxed for 15 min, whereupon tryptamine (8.0 g, 0.05 mol) was added and the reflux then continued for 30 min. After cooling the solution was poured into water (800 mL), and the solid formed was treated with hot methanol to yield crystals of **5**, yield 17.3 g (97%), mp 178–180 °C. The analytical sample (mp 180–181 °C) was recrystallized from dimethyl sulfoxide: IR 3348, 1678, 1612, 1398, 1313, 1200, 1144, 1122, 777, 751 $cm^{-1}$; MS, $m/z$ (relative intensity) 357 ($M^+$, 2), 227 (1), 214 (2), 197 (3), 149 (10), 145 (4), 144 (12), 143 (100), 131 (5), 130 (46), 129 (4), 128 (3).

**13b-(Trifluoromethyl)-13b,14-dihydrorutaecarpine (6).** Compound **5** (7.14 g, 0.02 mol) was refluxed in a mixture of acetic acid (30 mL) and hydrochloric acid (5 mL) for 30 min. The resulting mixture was diluted with water (20 mL) and the solid collected, washed with water, and dried, yield 7.10 g (99%), mp 270 °C dec: IR 3338, 1632, 1619, 1588, 1523, 1404, 1168, 962, 745, 738, 697 $cm^{-1}$; MS, $m/z$ (relative intensity) 357 (0.2), 356 (0.2), 288 (15), 287 (100), 286 (100), 285 (14), 273 (1), 257 (2), 256 (2), 168 (2), 166 (2), only peaks above $m/z$ 150 and stronger than 1% (except the $M^+$ and $(M-1)^+$ peaks) are listed, strongly doubly charged ions ($m/2z$) appeared around 143.5 mu.

**Rutaecarpine (1).** 13b-(Trifluoromethyll)-13b,14-dihydrorutaecarpine (7.14 g, 0.02 mol) was added to a hot well-stirred solution of KOH (4.0 g) in ethanol (50 mL) and water (15 mL). The starting material gradually went into solution, and after ca. 10 min a clear solution was obtained from which suddenly rutaecarpine appeared as needles. The reflux was continued for 15 min, whereupon the mixture was cooled and the crystals were collected, washed, and dried, yield 5.51 g (96%), mp 258–259 °C (lit.[34a] mp 262–263 °C): IR (in agreement with lit. data[34a,56]); MS (in agreement with lit. data[11b,56]).

**3-[2-(5-Methoxy-3-indolyl)ethyl]-2-(trifluoromethyl)-4(3*H*)-quinazolinone (25c).** The procedure given for **5** was followed using 5-methoxytryptamine as starting material, yield 85%, mp 199–201 °C: IR 3378, 1687, 1488, 1399, 1201, 1147, 1119, 773 $cm^{-1}$; MS, $m/z$ (relative intensity) 387 ($M^+$, 6), 227 (1), 214

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(1), 197 (2), 174 (11), 173 (86), 161 (7), 160 (100), 145 (21), 130 (19), 117 (16).

**10-Methoxy-13b-(trifluoromethyl)-13b,14-dihydrorutaecarpine.** The procedure given for **6** was followed using **25c** as starting material, yield 94%, mp 160 °C: IR 3350, 1645, 1611, 1491, 1162, 798, 759 $cm^{-1}$; MS, $m/z$ (relative intensity) only three significant peaks were observed 403 ($M^+$, 3), 334 (M − $CF_3$, 100), 333 (M − $CF_3H$, 63).

**Hortiacine (16a).** The procedure described for rutaecarpine was followed using 10-methoxy-13b-(trifluoromethyl)-13b,14-dihydrorutaecarpine as starting material, yield 98%, mp 252–253 °C (lit.[42] mp 252 °C): IR 3338, 1648, 1611, 1491, 1461, 1394, 1213, 1162, 1098, 1026, 798, 761 $cm^{-1}$; MS, $m/z$ (relative intensity) 318 ($M^+$ + 1, 19), 317 ($M^+$, 100), 302 (23), 284 (22), no further significant (stronger than 1%) peaks were observed.

**3-[2-(3-Indolyl)ethyl]-6,7-(methylenedioxy)-2-(trifluoromethyl)-4(3*H*)-quinazolinone.** The procedure given for **5** was followed using 3,4-(methylenedioxy)isatoic anhydride,[57] yield 95%, mp 250–252 °C: IR 3355, 1668, 1629, 1590, 1478, 1467, 1431, 1319, 1232, 1202, 1148, 1138, 1032, 1024, 934, 964, 743 $cm^{-1}$.

**3,4-(Methylenedioxy)-13b-(trifluoromethyl)-13b,14-dihydrorutaecarpine.** The procedure given for rutaecarpine (1) was followed using 3-[2-(3-indolyl)ethyl]-6,7-(methylenedioxy)-2-(trifluoromethyl)-4(3*H*)-quinazolinone as starting material, yield 97%, mp 270 °C dec: IR 3320 (b), 1641, 1604, 1549, 1475, 1388, 1306, 1270, 1178, 1163, 1042, 962, 938, 749, 732 $cm^{-1}$; MS, $m/z$ (relative intensity) only three significant peaks were obtained ($M^+$ 401, M − $CF_3$, and M − $CF_3H$) 401 ($M^+$, 9), 331 (M − $CF_3$)$^+$, 57%).

**Euxylophoricine C (17).** 3,4-(Methylenedioxy)isatoic anhydride[57] (2.07 g, 0.01 mol) was added to a solution of 2-(trifluoromethyl)-4*H*-3,1-benzoxazin-4-one[58] (2.15 g, 0.01 mol) in pyridine (20 mL). The mixture was refluxed for 40 min, whereupon the solvent was removed under reduced pressure. The residue was dissolved in a mixture of acetic acid (20 mL) and hydrochloric acid (6 mL) and refluxed for 60 min, whereupon the solvent was removed. The residue now obtained was heated (100 °C, 20 min) with a mixture of dimethyl sulfoxide (20 mL), water (3 mL), and KOH (2.0 g). Addition of water (50 mL) yielded the title compound, yield 3.15 g (91%), mp 310–312 °C (lit.[59] mp 310.5–312 °C): IR 3345, 1653, 1631, 1598, 1471, 1331, 1228, 1131, 729 $cm^{-1}$.

This product was identical with a sample kindly provided by Prof. B. Danieli.

**3-[2-(3-Indolyl)ethyl]-6,7-dimethoxy-2-(trifluoromethyl)-4(3*H*)-quinazolinone.** The procedure given for **5** was followed using 3,4-dimethoxyisatoic anhydride.[60] The reflux time in the first step was prolonged to 30 min and the second to 45 min. Yield 94%, mp 247–249 °C.

**3-[2-(5-Methoxy-3-indolyl)ethyl]-6,7-dimethoxy-2-(trifluoromethyl)-4(3*H*)-quinazolinone.** The procedure indicated above was used: yield 94%, mp 229–232 °C: IR 3360, 1673, 1611, 1502, 1406, 1232, 1215, 1197, 1032 $cm^{-1}$.

**2,3-Dimethoxy-13b-(trifluoromethyl)-13b,14-dihydrorutaecarpine (22b).** 3-[2-(3-Indolyl)ethyl]-6,7-dimethoxy-2-(trifluoromethyl)-4(3*H*)-quinazolinone (4.17 g, 0.01 mol) was refluxed in a mixture of acetic acid (30 mL) and hydrochloric acid (5 mL) for 2 h. The resulting mixture was diluted with water (20 mL) and the solid formed collected, washed with water, and recrystallized from ethanol, yield 3.82 g (89%), mp 260 °C dec: IR 3355, 1636, 1618, 1583, 1535, 1516, 1466, 1276, 1233, 1172, $cm^{-1}$; MS, $m/z$ (relative intensity) 417 ($M^+$, 10), 349 (29), 348 (M − $CF_3$, 100), 333 (9), 332 (20), 304 (7), only peaks stronger than 5% above $m/z$ 150 are listed.

**2,3,10-Trimethoxy-13b-(trifluoromethyl)-13b,14-dihydrorutaecarpine.** The procedure indicated above was used, yield 82% mp 250 °C dec.

**Euxylophoricine A (16b).** Compound **22b** (2.30 g, 0.005 mol) was heated with a mixture of dimethyl sulfoxide (25 mL), water (4 mL), and KOH (2.0 g) for 2 h at 100 °C. Addition of water yielded the title compound, yield 1.58 g (91%), mp 294–295 °C (lit. mp[62,59] 295, 296–298 °C): $^{13}C$ NMR 159.7 (s, C=O), 154.5 (s), 148.2 (s), 144.0 (s), 143.2 (s), 138.5 (s), 127.3 (s), 125.0 (s), 124.3 (d), 119.7 (2 d), 116.8 (s), 113.7 (s), 112.4 (d), 107.1 (d), 106.0 (d), 55.8 (2q), 37.6 (t), 18.9 (t) ppm.

**Euxylophoricine D (16c).** The procedure indicated above was used, yield (95%), mp 291–292 °C (lit.[61] mp 293): IR 3365, 1652, 1612, 1492, 1460, 1292, 1230, 1097, 818 $cm^{-1}$; $^{13}C$ NMR 159.7 (s, C=O), 154.4 (s), 153.6 (s), 148.0 (s), 144.0 (s), 143.2 (s), 133.6 (s), 127.5 (s), 125.0 (s), 116.3 (s), 115.4 (d), 113.5 (s), 113.2 (d), 105.8 (d), 100.3 (d), 55.6 (2 q), 38.0 (t), 18.9 (t) ppm.

**3-[2-(3-Indolyl)ethyl]-2-methyl-4(3*H*)-quinazolinone (25a).** Tryptamine (8.0 g, 0.05 mol) and 2-methyl-4*H*-3,1-benzoxazin-4-one (8.05 g, 0.05 mol)[24b] were heated (205 °C, 90 min). The cooled melt recrystallized from acetonitrile gave **25a**, yield 13.5 g (89%), mp 180–181 °C: IR 3340, 166, 1608, 1591, 1572, 1473, 1388, 778, 738 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.42 (s, 3 H, $CH_3$), 3.20 (t, $J$ = 7 Hz, 2 H, $CH_2$), 4.33 (t, 2 H, $J$ = 7 Hz, $NCH_2$), 6.90 (d, 1 H, $J$ = 0.5 Hz, indole α-H), 7.1–7.7 (m, 7 H, 7 Ar H), 8.32 (dd, 1 H, $J_o$ = 7, $J_m$ = 1.5 Hz, 5-H), 8.6 (br s, 1 H, NH).

**3-[2-(3-Indolyl)ethyl]-2-phenyl-4(3*H*)-quinazolinone (25b).** The procedure above was used starting with 2-phenyl-4*H*-3,1-benzoxazinone,[24b] yield 94%, mp 275–277 °C: IR 3355, 3050 (w), 1668, 1607, 1586, 1568, 1446, 1379, 1355, 1336, 1236, 1108, 1012, 779, 768, 742, 702 $cm^{-1}$.

**2-(Trichloromethyl)-4*H*-3,1-benzoxazin-4-one.** *N*-(Trichloroacetyl)anthranilic acid[63] (26.7 g, 0.1 mol) was refluxed with acetic anhydride (150 mL) for 3 h, whereupon the solvent was removed and the residue distilled (110–115 °C (0.3 mm)), yield 20.0 g (80%), mp 98–100 °C (lit.[64] mp 98–100 °C).

***N*-(2-[(Trichloroacetyl)amino]benzoyl)tryptamine (10a).** A solution of tryptamine (1.60 g, 0.01 mol) and 2-(trichloromethyl)-4*H*-3,1-benzoxazin-4-one (2.65 g, 0.01 mol) in pyridine (15 mL) was refluxed for 2 h, the solvent removed, and the residue crystallized from 2-propanol, yield 3.12 g (74%), mp 147–149 °C: IR 3360, 3287, 3191, 1701, 1641, 1608, 1515, 1452, 823, 762, 753, 748, 673 $cm^{-1}$.

**Reaction of Tryptamine with 2-(Trichloromethyl)-4*H*-3,1-benzoxazin-4-one at 175 °C.** Tryptamine (1.60 g) and 2-(trichloromethyl)-4*H*-3,1-benzoxazin-4-one (2.65 g) were heated (175 °C, 3 h), whereupon the dark reaction mixture was chromatographed on silica gel using $CH_2Cl_2$ (with slowly increasing amounts of $CH_3OH$) as eluent. The following three compounds were identified: 3-[2-(3-Indolyl)ethyl]-2-(trichloromethyl)-4-(3*H*)quinazolinone (**11**), yield 8%, mp 176–177 °C. *N*-(2-[(Trichloroacetyl)amino]benzoyl)tryptamine (**10a**), yield 12%. 3-[2-(3-Indolyl)ethyl]-2,4-quinazolinedione (**12a**), yield 68%.

**3-[2-(3-Indolyl)ethyl]-1-methyl-2,4-quinazolinedione (12b).** *N*-(2-Aminobenzoyl)-*N*-methyltryptamine (**33b**) (2.93 g, 0.01 mol) was refluxed in methyl chloroformate (20 mL) for 6 h. Upon evaporation the residue was treated with a solution (60 °C) composed of ethanol (20 mL), water (10 mL), and KOH (2.0 g). The solid formed was collected and recrystallized from ethanol, yield 2.40 g (75%), mp 216–218 °C: IR 3332, 1696, 1650, 1613, 1488, 1433, 1398, 1355, 858, 847 $cm^{-1}$.

**3-[2-(3-Indolyl)ethyl]-2,4-quinazolinedione (12a).** The procedure given above was used starting with compound **18**, yield (82%), mp 305–307 °C: IR 3350 (br), 2900 (br), 1705, 1635, 1448, 1409, 1337, 1286, 1092, 995, 739 $cm^{-1}$.

***N*$^1$-(2-(Carbomethoxyamino)benzoyl)tryptamine (10b).** The procedure given for **12a** was used but the treatment with hot alkali was omitted and the reaction mixture was instead neutralized at 25 °C with $K_2CO_3$. This procedure afforded **10b**, yield (95%), mp 173–174 °C: IR 3422, 3320, 1748, 1638, 1595, 1526, 1452, 1247, 1219, 1062, 753, 742 $cm^{-1}$.

Treatment of **10b** (as well as **10a**) with water, EtOH, and KOH (60 °C) yielded **12a**.

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**13b-(Trifluoroacetyl)-13b,14-dihydrorutaecarpine (20).** Trifluoroacetic anhydride (2.10 g, 0.01 mol) in acetonitrile (10 mL) was added to a stirred mixture of 3-[2-(3-indolyl)ethyl]-4-(3*H*)-quinazolinone (**19**) (2.89, 0.01 mol) in acetonitrile at 1–2 °C. A clear solution was formed, which soon deposited crystals of the product, which was collected after 2 h at 1–2 °C, yield 3.30 g (86%), mp 215 °C dec: IR 3283, 1734, 1646, 1473, 1204, 1155, 857, 844 $cm^{-1}$; MS, *m/z* (relative intensity) 385 ($M^+$, 21), 316 (6), 287 (8), 215 (23), 171 (11), 170 (62), 169 (100), 147 (10), 146 (92), 144 (11), 143 (21), 115 (21), 90 (31).

**13b,14-Dihydrorutaecarpine (21).** 13b-(Trifluoroacetyl)-13b,14-dihydrorutaecarpine (1.92 g, 0.005 mol) was refluxed (5 min) in ethanol (18 mL) containing water (2.5 mL) and KOH (3.0 g). A clear solution was formed quickly, which on cooling gave crystals of the product, yield 1.41 g (98%), mp 226–228 °C (lit.[8] mp 227–230 °C): IR in agreement with literature[8] data.

**14-Formyl-13b,14-dihydrorutaecarpine (40). Method A.** 13b,14-Dihydrorutaecarpine (**21**) (289 mg, 1 mmol) was stirred with formic acetic anhydride (5 mL) at 25 °C for 3 h, whereupon the new crystals formed were collected, washed with cold methanol and dried, yield 305 mg (96%), mp 285–287 °C (lit.[8] mp 282–283 °C).

**Method B.** 3-[2-(3-Indolyl)ethyl]-4(3*H*)-quinazolinone (**19**) (578 mg, 2 mmol) in formic acetic anhydride (10 mL) was heated slowly (1 h) from 25 to 60 °C and kept at this temperature for 5 min. The solution was allowed to cool and the crystals formed were collected, washed with cold methanol, and dried, yield 480 mg (76%), mp 285–287 °C: IR 3342, 2918, 1690, 1608, 1493, 1472, 1413, 1378, 1327, 1318, 1302, 1282, 1240, 868, 771, 761, 747, 702 $cm^{-1}$; MS, *m/z* (relative intensity) 318 (4), 317 ($M^+$, 16), 289 (11), 288 (52), 287 (100), 286 (53), 170 (22), 169 (62), 148 (11), 147 (9), 146 (18), 143 (13).

**Hydrolysis of 14-Formyl-13b,14-dihydrorutaecarpine (40).** Compound **40** (316 mg, 1 mmol) was refluxed (15 min) in ethanol (2.5 mL) containing water (0.5 mL) and KOH (0.8 g). A clear solution was quickly formed, which on cooling yielded crystals of 13b,14-dihydrorutaecarpine (**21**), 195 mg (67%), mp 226–228 °C.

**7,8-Dehydrorutaecarpine (30).** DDQ (454 mg, 0.002 mol) in dioxane (10 mL) was added to a hot solution of rutaecarpine (**1**, 574 mg, 0.002 mol) in dioxane (50 mL). After a reflux period (30 min) the solvent was removed and the residue extracted with a solution of KOH (1.5 g) in water (25 mL). This procedure was repeated until all DDQ-2H had been removed. The residue was purified by sublimation (220 °C, 0.5 mm), yield 430 mg (75%), mp 280–281 °C (lit.[56] mp 280–281 °C):[65] IR in agreement with reported data.

**Dehydrogenation of 13b,14-Dihydrorutaecarpine with DDQ.** The procedure given above was repeated starting with DDQ (454 mg, 0.002 mol) and 13b,14-dihydrorutaecarpine (289 mg, 0.001 mol) to give 7,8-dehydrorutaecarpine, yield 75%, mp 280–281 °C.

**Synthesis of Compound 26.** Trifluoroacetic anhydride (20 mL) was added during 5 min to a stirred mixture of 2-methyl-4(3*H*)-quinazolinone (8.1 g, 0.05 mol) and acetonitrile (40 mL). A clear solution was quickly formed, which after a reflux period (3 h) and cooling deposited crystals, yield 8.9 g (51%), mp 292–294 °C: IR 3190 (NH, br), 1714 (C=O), 1629 (C=O), 1587, 1283, 1210, 1191, 1166, 1140, 912, 848, 867, 773 $cm^{-1}$; MS, *m/z* (relative intensity) 352 ($M^+$, 28), 333 (M – F, 8), 284 (M + 1 – $CF_3$, 14), 285 (M – $CF_3$, 100), 213 (M – $CF_3$ – $HCF_3$, 57), 145 (81), 144 (35).

**Isoevodiamine Methosulfate (31a).** Compound **19** (2.89 g, 0.02 mol) was dissolved in hot dioxane (30 mL), whereupon dimethyl sulfate (1.05 mL, 0.11 mol) in dioxane (5 mL) was added dropwise. Crystals soon started to deposit and the reflux period was continued (2 h) until no more crystals were formed. After cooling and washing with dioxane the crystals were collected and dried in an exsiccator, yield 4.02 g (97%) mp 240–245 °C: IR 3260, 1715, 1662, 1258, 1243, 1221, 1009, 768, 762 $cm^{-1}$.

**Isoevodiamine (33a). Method A.** Isoevodiamine methosulfate (**31a**, 4.15 g) dissolved in hot water was allowed to cool whereupon a solution of KOH in water was added. The free base formed was collected and recrystallized from methanol/water, yield 2.45 g (76%), mp 114–115 °C (lit.[12] mp 113 °C): IR 3360, 3308, 1657, 1603, 1527, 1365, 780, 746 $cm^{-1}$.

**Method B.** *N*-(2-Aminobenzoyl)-*N*-methyltryptamine (**33c**, 2.93 g, 0.01 mol) was dissolved in acetic formic anhydride (10 mL) at 30 °C. Crystals of **33a** appeared after ca. 45 min. After 2 h the mixture was slowly cooled (finally to –30 °C) and the crystals obtained were washed with cooled methanol/water, yield 2.73 g (85%), mp 114–115 °C.

**Evodiamine (2).** Isoevodiamine (**33b**, 3.03 g, 0.01 mol) was refluxed with acetic anhydride (10 mL) for 1 h. The crystals formed on cooling were collected, washed with methanol, and dried, yield 2.65 g (87%), mp 269–271 °C (lit.[11b,31] mp 268–270, 268 °C): IR in agreement with literature data; MS in agreement with literature[11b] data.

A sample of evodiamine[31] kindly provided by Professor Danieli was identical with our product.

**3-[2-(3-Indolyl)ethyl]-1-methyl-1,2-dihydro-4(3*H*)-quinazolinone.** The methosulfate **31a** (415 mg) and $NaBH_4$ (0.4 g) were stirred in methanol (40 mL) for 1 h at 25 °C, whereupon water was added and the solid formed collected, dried and recrystallized from methyl acetate/diisopropyl ether, yield 250 mg (83%), mp 144–145 °C (lit.[27] mp 141 °C): IR 3245, 1628, 1602, 1489, 1460, 1434, 1383, 1272, 1230, 753, 742 $cm^{-1}$.

**Synthesis of Compound 33b.** Compound **33a** (2.93 g, 0.01 mol) in dioxane (25 mL) was treated with TFAA (1.68 mL, 0.012 mol) at 25 °C for 2 h. Water was added and the solid formed recrystallized from toluene, yield 3.50 g (80%), mp 119–120 °C: IR 3340, 1698, 1640, 1532, 1440, 1340, 1020, 830, 710 $cm^{-1}$.

***N*-(Trifluoroacetyl)tryptamine (45).** Tryptamine (1.60 g, 10 mmol) was refluxed with ethyl trifluoroacetate (1.19 mL, 10 mmol) in dioxane (20 mL) for 6 h, whereupon the solvent was removed and the oily residue crystallized from *i*-PrOH/$H_2O$, yield 1.42 g (55%), mp 102–103 °C: IR 3395, 3318, 3055, 1699, 1559, 1448, 1204, 1170, 747 $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$) 156.6 (q, C=O), 136.3 (s, C-7a), 127.2 (s, C-3a), 122.8 (d, C-2), 121.0 (d, C-6), 118.4 (d, C-5), 118.1 (d, C-4), 115.5 (d, C-7), 111.1 (s, C-3), 115.5 (q, $CF_3$), 24.38 (t, $CH_2$), 38.7 (t, $NCH_2$) ppm.

**Cleavage of Compound 33b.** Compound **33b** (2.5 g) was refluxed in toluene (35 mL) for 6 h, whereupon the solvent was evaporated and the residue chromatographed on silica gel using $CH_2Cl_2$ containing slowly increasing amounts of $CH_3OH$. The following two compounds were isolated.

**5,11-Dimethyldibenzo[*b*,*f*]-1,5-diazocine-6,12-dione (*N*,*N*-dimethyldianthranilide) (46):** yield 85%, mp 205–207 °C (lit.[44a] 205–207, lit.[59] 193–195, lit.[44b] 206–207, lit.[44c] 203–205 °C).

***N*-(Trifluoroacetyl)tryptamine (45):** yield 85%, mp 102–103 °C.

**6,8-Dichloro-2-(trifluoromethyl)-4-oxazinone (44c).** 3,5-Dichloroanthranilic acid (20.6 g, 0.1 mol) was dissolved (at 25 °C) in dioxane (80 mL) containing trifluoroacetic anhydride (16.8 mL, 0.12 mol). The clear solution was then refluxed for 1 h and the solvent evaporated. The residue was then refluxed in acetic anhydride (60 mL) for 3 h. After evaporation of the excess of $Ac_2O$ the (solid) residue was recrystallized from diisopropyl ether, yield 22.7 g (80%), mp 113–114 °C: IR 3082, 1783, 1678, 1589, 1562, 1447, 1348, 1249, 1194, 1153, 1111, 1048, 878, 782 $cm^{-1}$.

The following compounds were prepared similarly.

**6-Chloro-2-(trifluoromethyl)-4-oxazinone (44b):** yield (76%), mp 54–55 °C.

**6,7-Dimethoxy-2-(trifluoromethyl)-4-oxazinone (44a):** yield 88%, mp, 143–144 °C.

**3-Chlororutaecarpine (16e).** 6-Chloro-2-(trifluoromethyl)-4-oxazinone (4.97 g, 0.02 mol) and tryptamine (3.20 g, 0.02 mol) were heated (190 °C, 1 h) under nitrogen. The melt obtained was dissolved in acetic acid (20 mL) containing concentrated HCl (aqueous 3 mL) and refluxed for 0.5 h whereupon the solvent was evaporated and the residue treated with hot ethanol (25 mL) containing water (5 mL) and KOH (3.0 g) for 1 h. The crystals formed were collected and dried, 6.37 g (99%), mp 314–316 °C: IR 3295, 1662, 1613, 1597, 1546, 1471, 1332, 1226, 828, 732 $cm^{-1}$; MS, *m/z* (relative intensity) 324 (5), 323 (25), 322 (31), 321 (100), 320 (61), 319 (4), 287 (6), 286 (7), 285 (9), 257 (5), all peaks above 4% are listed.

**1,3-Dichlororutaecarpine (16d).** The general procedure given above was used, yield 98%, mp 308–310 °C.

(65) A lower melting point (154–155 °C) reported[38] for **30** seems to be in error. Repetition of the experiment[38] yielded in fact **30**, with the correct mp 280–281 °C.

**2-(Trifluoromethyl)-4(3*H*)-quinazalinone (47).** Anthranilic amide (13.6 g, 0.1 mol) and trifluoroacetic anhydride (16.8 mL, 0.12 mol) in dioxane (50 mL) were stirred at 25 °C for 1 h whereupon the solvent was evaporated to yield *N*-(trifluoroacetyl)anthranilic amide (a known[66] compound), which was cyclized to the title compound by reflux (2 h) in acetic acid or (for small samples) by sublimation at 210 °C, yield 14.8 g (69%), mp 253–254 °C (lit.[67,68] mp 249–250 °C).

**2,2-Bis(trifluoromethyl)-1,2-dihydro-4(3*H*)-quinazolinone (48).** Anthranilic amide (13.6 g, 0.1 mol) and hexafluoroacetone hydrate (15 mL) in dioxane (50 mL) were refluxed for 2 h, whereupon the solvent was evaporated and the residue purified by sublimation (yielding centimeter-big crystals) or by recrystallization from aqueous ethanol, yield 19.4 g (71%), mp 110–112 °C: IR 3315, 3265, 1754, 1623, 1518, 1491, 1326, 1305, 1274, 1243, 1228, 1217, 1185, 1161, 1122, 1086, 976, 751, 718, 688 $cm^{-1}$; $^{13}C$ NMR, see the NMR chart.

**Synthesis of Compound 29.** 4(3*H*)-Quinazolinone (2.92 g, 0.02 mol) and 2-methylindole (2.62 g, 0.02 mol) were refluxed in acetic anhydride (35 mL) for 4 h. Excess of $Ac_2O$ was then evaporated and the residue treated with methanol yielded crystals of **29**, 5.51 g (77%), mp 232–234 °C: IR 3260 (NH, br), 1711, 1695, 1649, 1608, 1491, 1468, 1372, 1309, 1242, 763, 748 $cm^{-1}$; MS, *m/z* (relative intensity) 361 ($M^+$, 24), 318 (8), 277 (11), 276 (100), 158 (35), 146 (38), 131 (40), 130 (100), only diagnostic peaks above *m/z* 100 are listed; $^{13}C$ NMR 171.1 (C=O), 168.9(C=O), 163.1 (C=O), 61.1 (d), 27.1 (q, $NCOCH_3$), 22.5 (q, $NCOCH_3$), 11.9 (q, indolic 2-$CH_3$) ppm, in addition 14 signals from the aromatic carbon atoms were observed between 139.4 and 105.3 ppm.

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# Structures and Stereochemistries of Oscillatoxin B, 31-Noroscillatoxin B, Oscillatoxin D, and 30-Methyloscillatoxin D

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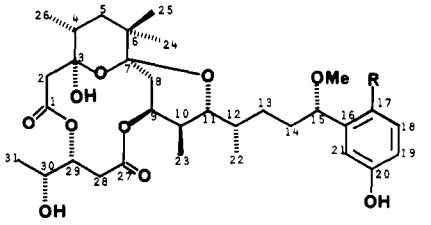
Four aplysiatoxin-related compounds, viz., oscillatoxin B (**3**), 31-noroscillatoxin B (**5**), oscillatoxin D (**6**), and 30-methyloscillatoxin D (**4**), have been isolated from marine blue-green algae belonging to Oscillatoriaceae. The structures and stereochemistries have been determined by spectral studies and chemical degradation. Oscillatoxin B was shown to be a mixture of the C-4 isomers B1 (**3a**) and B2 (**3b**).

The marine blue-green alga *Lyngbya majuscula* (Oscillatoriaceae) is the causative agent of a severe contact dermatitis in Hawaii[3] and Okinawa.[4] Two substances, aplysiatoxin (**1**) and debromoaplysiatoxin (**2**), which account for the highly inflammatory response associated with this dermatitis, have been isolated from *L. majuscula*,[5,6]




**1** R = Br
**2** R = H

as well as from the digestive gland of the seahare *Stylocheilus longicauda*,[7] a gastropod mollusk that feeds

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