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Thionation of tryptanthrin, rutaecarpine and related molecules with a reagent prepared from P_4S_{10} and pyridine.

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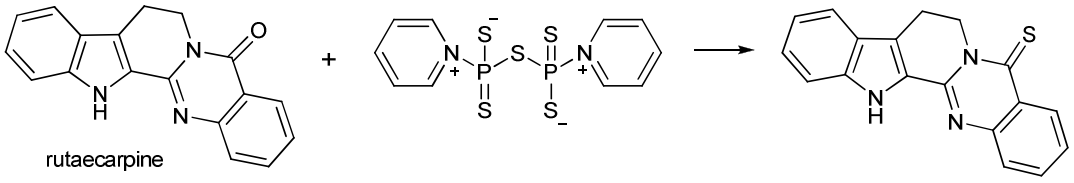


ABSTRACT: Reaction of P_4S_{10} in hot pyridine produces a crystalline solid which can be collected and used for thionations in other solvents such as acetonitrile and sulfolane. The biologically active natural products tryptanthrine, rutaecarpine, 7,8-dehydrorutaecarpine and some related compounds have now been converted to thionated versions simply by heating the molecules with this thionating reagent in sulfolane (typically at 135 °C for 20 min) followed by a work-up in water. No chromatography was necessary.

INTRODUCTION

The reagent, a complex between the element P_2S_5 and pyridine, **7**, is readily prepared by

heating P_4S_{10} in pyridine for a short period of time (50 min).[1] The reagent is isolated as crystals and can readily be transferred to solvents such as acetonitrile and dimethylsulfone, and used for thionation of amides in a clean fashion. The work-up (addition to water) is simple, because any remaining reagent is converted to the water-soluble salt **11**. In the present paper these principles have been applied to the indole alkaloids tryptanthrin, rutaecarpine and 7,8-dehydrorutaecarpine plus some related molecules.

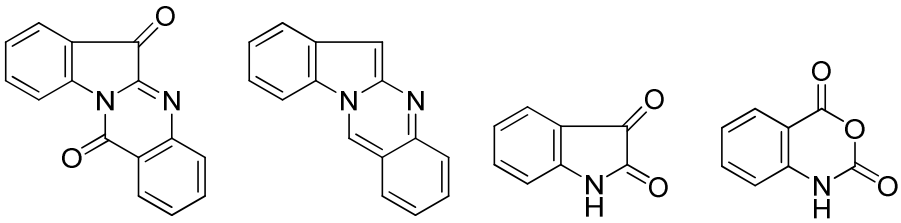
RESULTS AND DISCUSION

The brightly yellow compound 6,12-dihydro-6,12-dioxoindolo[2,1-*b*]quinazoline, **1** has been known as a synthetic compound at least since 1892.[2] In 1971 the trivial name tryptanthrin was coined by Zähner[3] and Fiedler[4,5] when **1** could be isolated from culture solutions of the yeast *Candida lipolytica*, which had been doped with large amounts of tryptophan and anthranilic acid. In 1977 tryptanthrin was identified as a natural product by Bergman when it was isolated from the fruits of the cannonball tree, *Couroupita quianensis*, Aubl.[6] Subsequently, Honda et al.[7-9] identified tryptanthrin as the active principle in the leaves of *Strobilanthes cusia* o. Kantze, which has a long tradition in Okinawa as a remedy against dermatophytic infections, notably athlete's foot. Tryptanthrin has a manifold of other interesting biological activities. For example, Yang et al.[10] have reported therapeutic activity against Lewis lung cancer tumor in a mouse model. Pitzer et al.[11] have reported activity against malaria, and Grundt has demonstrated interesting inhibition of *Toxoplasma gondii*[12] and a study by Hwang et al. featured antituberculosis activity.[13]

Tryptanthrin **1**, whose structure was established by X-ray crystallography as early as 1974,[14] has also undergone detailed NMR studies.[15] An extensive review by Tucker and Grundt is available[16]. The basic ring system **2** has been reviewed by Cava and Billimoria.[17] Tryptanthrin **1** is best synthesized by condensation of isatin **3** (a co-product from the cannonball tree)[6] and

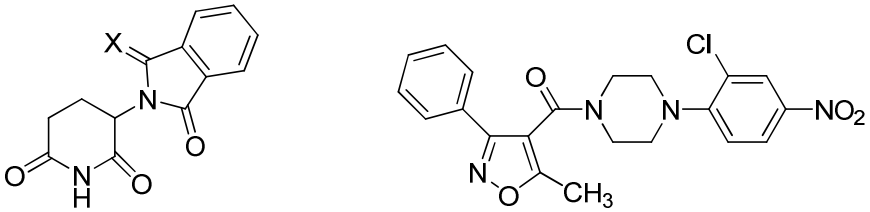
isatoic anhydride **4** with elimination of carbon dioxide.[18] (Figure 1) Older less attractive methods include oxidation of isatin with $KMnO_4$ and other oxydants.[12] Several of the more recently developed approaches to tryptanthrin are also rather unattractive like an electro-synthesis[19] starting with isatin and an approach involving *ortho*-lithiophenyl isocyanide.[20]

Figure 1. Structures of compounds **1**, **2**, **3,** and **4**.



There are several examples showing that thionation of biologically active molecules can lead to products with different and/or improved biological properties. Thus thionation of thalidomide **5a** gave a series of mono- di- and trithionated products e.g. **5b**.[21,22] It was found that **5b** effectively reduces the tumor necrosis factor TNF-α. The di- and trithionated derivatives were even more efficient in that respect.[22] Thionations of nucleosine **6**,[23] a molecule with interesting anti-influenza activity, gave an analogue with widened activity, including against H_1N_1.[24] (Figure 2)

Figure 2. Structures of compounds **5** and **6**.



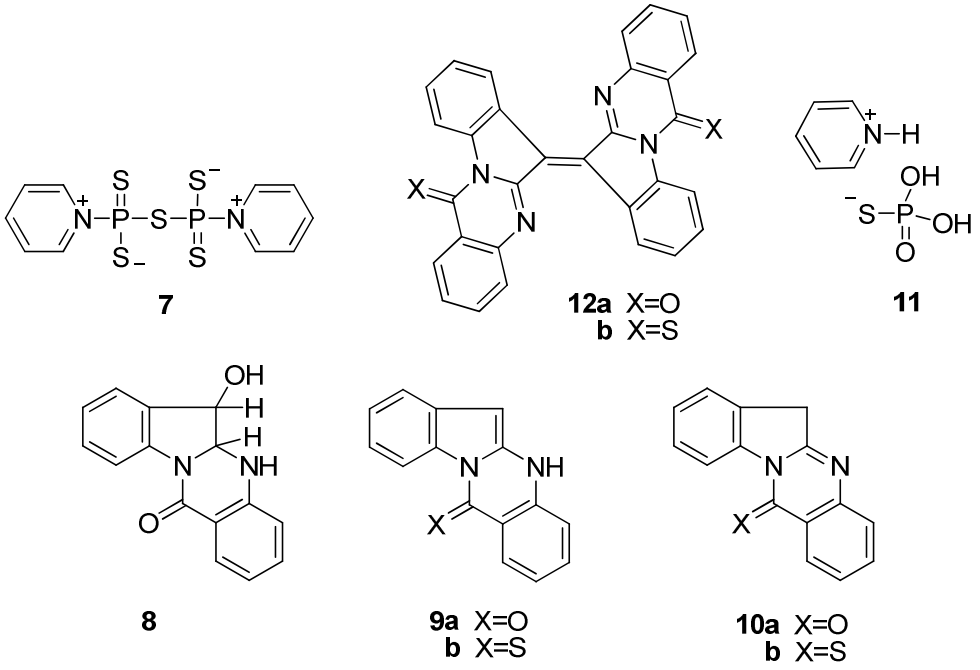
5a X=O
b X=S

6

We have recently developed a versatile technique for thionations based on the reagent **7** that

can be used over a wide range of temperatures (up to 180 °C). Useful solvents are acetonitrile and sulfolane.[1] Sulfolane is a dipolar aprotic industrial solvent commonly used in gas production and oil refining.[25] Sulfolane is also used as a versatile solvent for Friedel-Crafts reactions. The reagent **7** in sulfolane now has been applied to tryptanthrin and some of its reduced derivatives (**8** and **9a**), which both have been known for a long period of time.[26]

Figure 3. Structures of compounds **7**, **8**, **9**, **10**, **11**, and **12**.

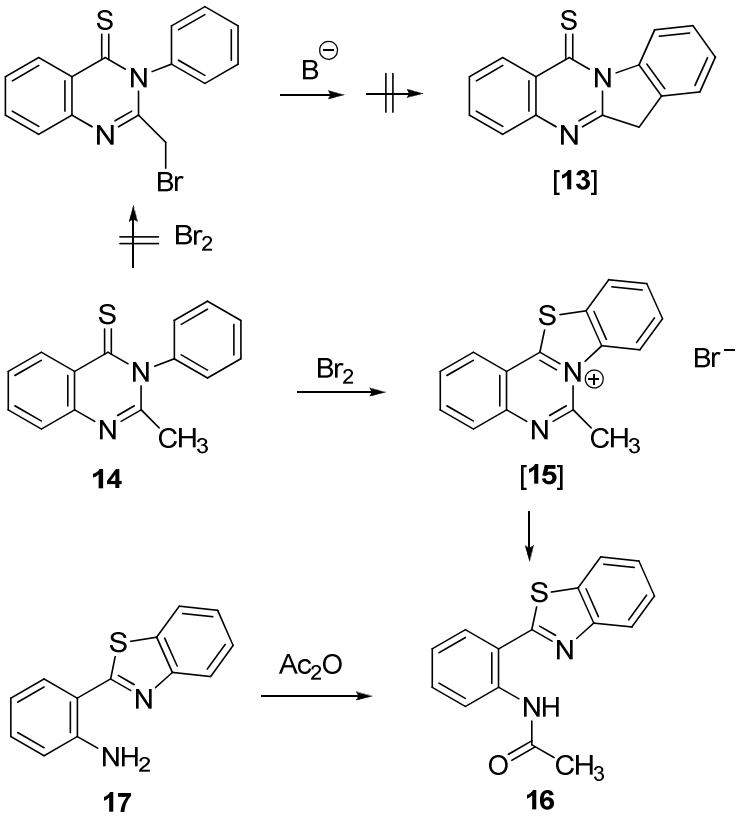


Tryptanthrin was heated for a short period (135 °C, 20 min) with the reagent **7** in sulfolane whereupon the cooled (30 °C) mixture was poured into water, which typically precipitates the product as a solid. Any remaining reagent will quickly decompose to the soluble salt **11**.[1] In the experiment just discussed the product is not dithionated tryptanthrin but the coupled product **12b**, which is a blackish compound of low solubility. Compound **12a** is known[26] and also yielded the highly insoluble **12b** on thionation. This manner of coupling observed is rather characteristic for this type of molecules.[26-30] Thionations of **9a** and **8** gave a mixture of the thionated tautomers **9b**

and **10b**, which could be separated by chromatography.[26] (Figure 3) In the ^{1}H NMR spectrum **9b** featured a 1H-singlet at 6.06 ppm, whereas its tautomer **10b** exposed a CH_2-singlet at 4.08 ppm. The non-thionated tautomeric pair **9a** *vs.* **10a** has previously been discussed in the literature.[26] In the solid state it exists as the imine tautomer **9a** but when dissolved in DMSO it exists exclusively as the amine tautomer **10a** but in $CDCl_3$ again as **9a**. Xia et al.[31] have likewise reported, without citing previous literature, that the amine tautomer is predominating in $CDCl_3$ (1H-doublet at 79.7 ppm).

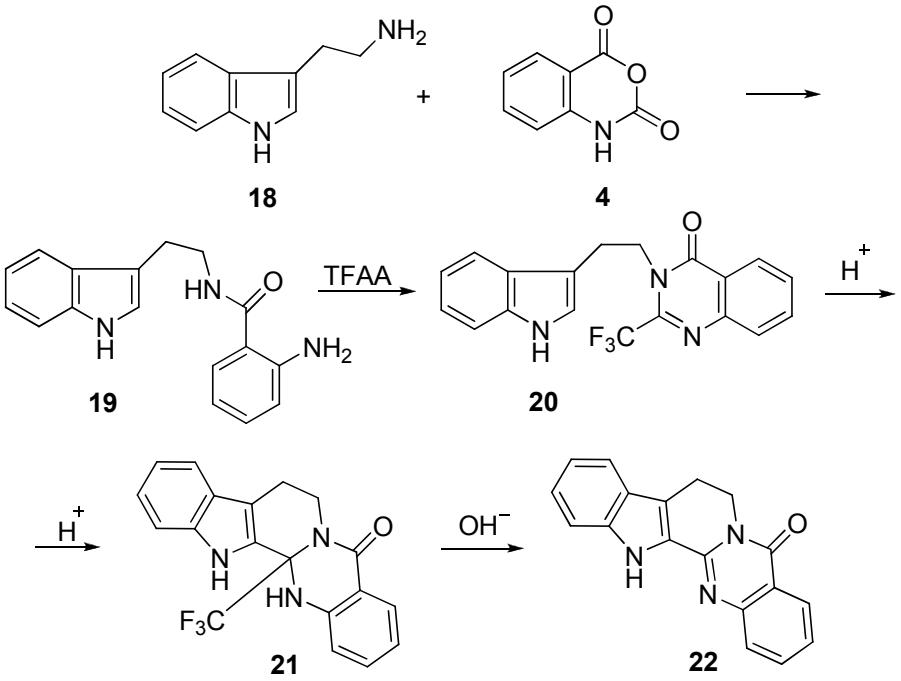
The properties of **10b** are in strong disagreement with a purported molecule previously reported to have this structure.[32] The literature experiment has now been repeated and the product has a totally different structure, namely **16** (Scheme 1). The starting material used, **14**, was not attacked by bromine on the methyl group but rather the sulfur atom was oxidized to an electrophilic species that attacked the phenyl group yielding the fused thiazolium system **15** that under the basic conditions used underwent a ring-opening, thus eventually yielding the known benzothiazole derivative **16**.[33,34] The parent compound, **17**, is also known. [33,34]

Scheme 1.



A multitude of biological activities have been reported for the indole alkaloid rutaecarpine **22** which can be isolated from the plant *Evodia rutaecarpa*. The biological activity of rutaecarpine includes anticancer effects, antithrombotic activity, anti-inflammatory and analgesic effects and several reviews are available.[35-38] Recently rutaecarpine has been claimed as a remedy against insomnia caused by caffeine, and is marketed under the name Rutaesomn.[39] An efficient and fast synthesis of rutaecarpine, as previously described by Bergman[40], starts from tryptamine, **18**, and isatoic anhydride, **4**, and is outlined in Scheme 2. In the ^{1}H NMR spectra rutaecarpine show the aliphatic protons as two triplets at 3.25 and 5.10 ppm, respectively.

Scheme 2



Rutaecarpine **22** could be readily thionated under standard conditions, i.e. reaction with the reagent **7** in sulfolane (135 °C, 20 min) followed by work-up in water, which yielded the desired product **23** as a bright yellow solid. The introduced thiono function featured a signal at 187.4 in the ^{13}C NMR spectrum. The product **23** was isolated as a 1:1 complex with sulfolane, which was quite stable but the solvent molecule could be removed by repeated recrystallizations from acetic acid. The intensity of the color was taken as an indication that **25** is an important resonance contributor to **24**.

When rutaecarpine was heated alone in sulfolane no complex was formed, indicating that the sulfone group is interacting with the thiono functionality of **24** as illustrated in figure 4.

Figure 4. 1:1 Complex between thionated rutaecarpine and sulfolane.

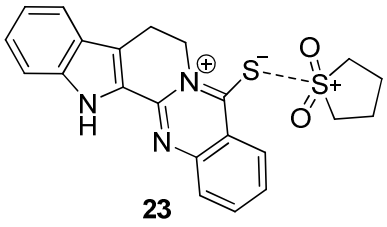
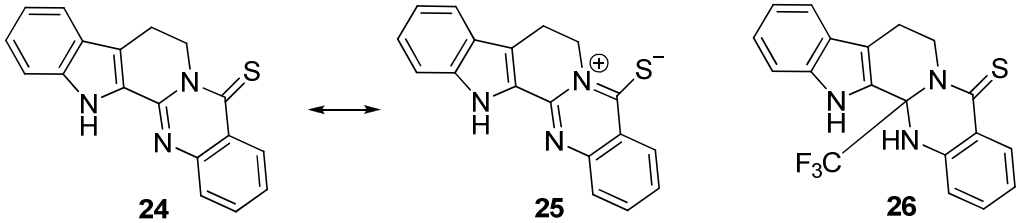


Figure 5. Resonance of the pair **24**, **25** and the structure of **26**.



The CF_3 group in **21** had a profound influence on the chemical shifts of the four aliphatic protons, all of them now widely separated between 6.46 and 2.88 ppm.

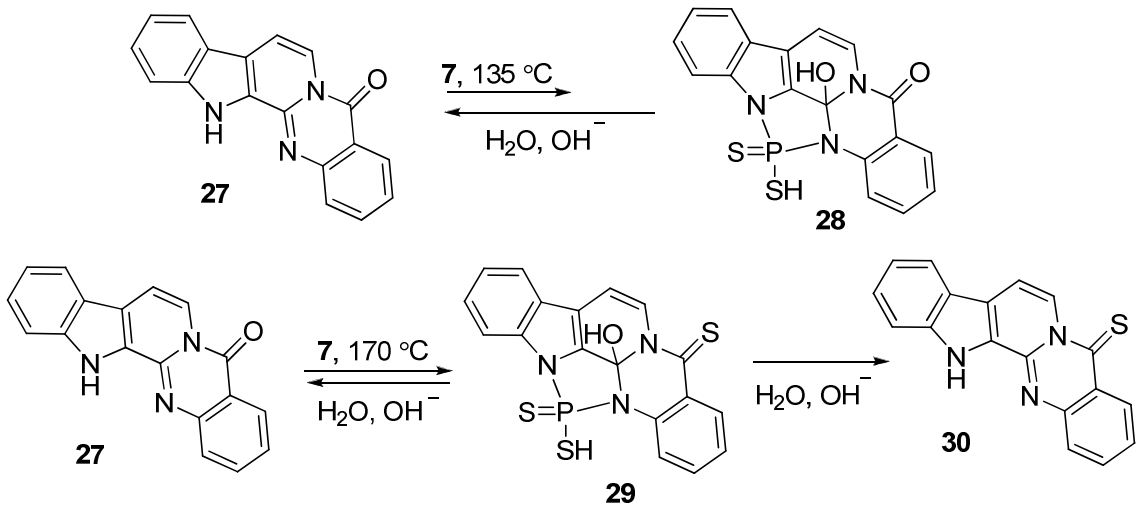
This CF_3-substitueted intermediate **21** was also thionated at 135 °C. It would not have been unexpected if elimination of trifluoromethane should have taken place. This was not the case and the thionated version of **21** was obtained, i.e. **26**, however when the reaction was performed at 165 °C elimination took place, i.e. **21** gave thionated rutaecarpine **24**. (Figure 5) In an additional experiment it was found that when **21** was heated at 240 °C the element of CF_3H was eliminated and rutaecarpine **22** was formed.

7,8-Dehydrorutaecarpine **27** is known as a congener with rutaecarpine and is synthetically available by dehydrogenation of rutaecarpine with 2,3-dichloro-4,5-dicyanoquinone (DDQ).[40] 7,8-Dehydrorutaecarpine has compared with rutaecarpine quite often more potent biological properties. [41-43], and the compound also has potential for treatment of Alzheimer's disease.[44]

Attempted thionation of 7,8-dehydrorutaecarpine **27** (ν C=O, 1671 cm^{-1}) gave a somewhat

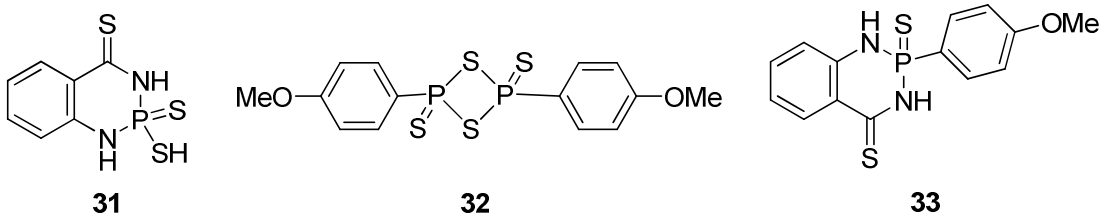
perplexing product with an IR absorption at 1732 cm^{-1}, clearly indicating an intact carbonyl group. This product could by further studies be assigned structure **28** wherein *N,N*-chelated phosphorus had been introduced. Mild basic hydrolysis (NaOH, EtOH, and H_2O) gave 7,8-dehydrorutaecarpine back.

Scheme 3



Compared with rutaecarpine (ν C=O, 1652 cm^{-1}) dehydrorutaecarpine (ν C=O, 1671 cm^{-1}) has a less nucleophilic amide function and a more nucleophilic N heteroatom. Hence an attack of the two N atoms is preferred over the amide bond. Quite a number of N,N-chelated complexes including phosphorus have been described in the literature.[45,46] Most of them have been obtained by using Lawesson's reagent **32**. Thus e.g. anthranilamide gave **33**. (Figure 6)

Figure 6 Structures of Lawesson's reagent **32** and the cyclized products **31** and **33**.



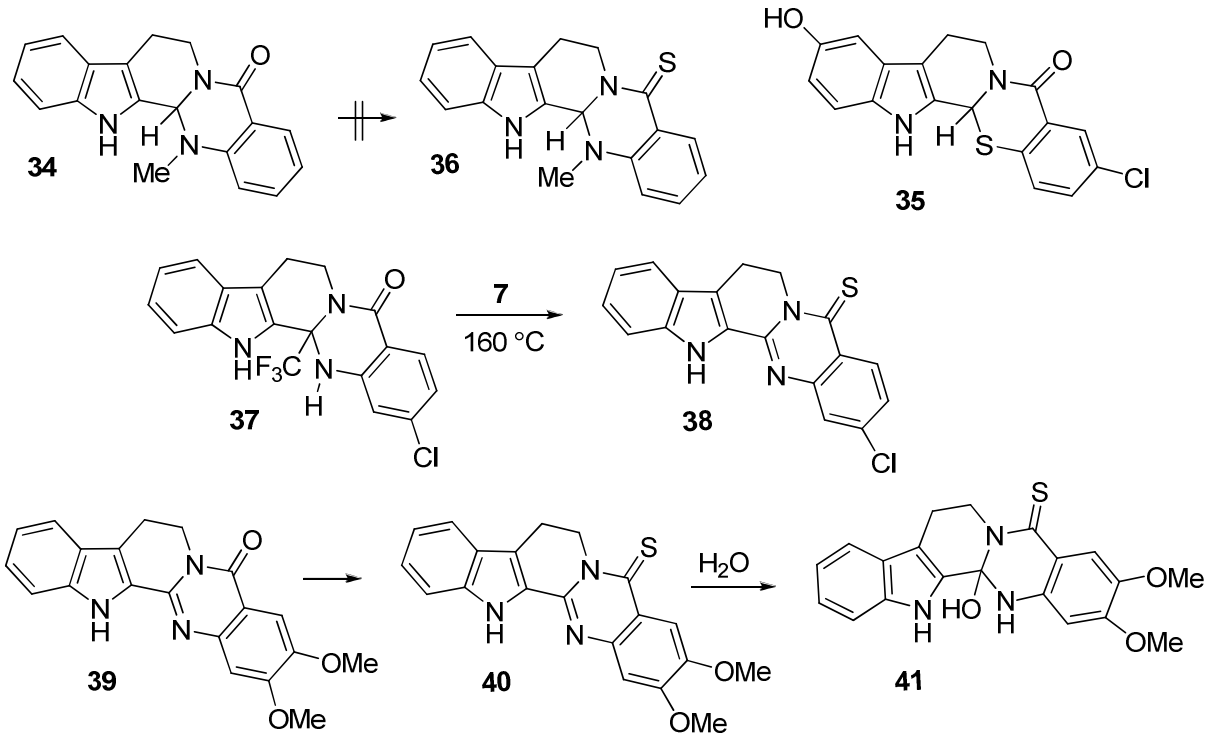
When 7,8-dehydrorutaecarpine was heated with the reagent **7** in excess at slightly higher

temperature the thionated molecule **29** was formed, which after mild hydrolysis gave the desired thionated compound **30** (Scheme 3).

Evodiamine **34** is a biologically interesting congener to rutaecarpine in *Evodia rutaecarpa*,[47] which improves cognitive abilities in transgenic mouse models of Alzheimer's disease.[48] Several analogues of evodiamine, notably the thio derivative **35**, show *in vitro* and *in vivo* antitumor efficacy.[49] Racemic evodiamine has resently been resolved.[50] In this context is should be noted that compound **21** is a trifluoro analogue of evodiamine.

Against this background thionated evodiamine should be an interesting molecule but unfortunately the attempted conversion **34**→**36** failed due to ring-cleavage reactions and also ready loss of the methyl group. The sensitivity of evodiamine against e.g. acids have been discussed by Daneili and Palmisani.[51]

Scheme 4



The thionation process could also be extended to substituted rutaecarpine derivatives, thus the 2-chloronated precursor **37** gave the thionated version of 2-chlororutaecarpine **38** in good yields, as did thionation of euxylophoricine A, **39** (to yield **40** and **41**), originally obtained from the commercially important tree yellowheart, *Euxylophora paraensis*. (Scheme 4) The nonplanar hydrate **41** featured, as expected, a complex pattern of the aliphatic protons in the ^{1}HNMR spectrum. 2-Chlor-orutaecarpine has been described in the literature[52] but the preparative method described there was not used. The route *via* **37** was preferred.

CONCLUSIONS

The reagent formed from P_4S_{10} and pyridine is a useful reagent for thionations, in a wide range of temperatures of amides and is preferably applied in sulfolane, where the process is quick. Work-up with water is easy and chromatographic purification is not necessary, as distinct from many thionations using Lawesson's reagent, which normally is not used above 110 °C.

EXPERIMENTAL SECTION

General information. NMR Data were recorded on a 300 or 500 MHz instrument, using the residual solvent signal as reference. Throughout the work $DMSO_{-d6}$ was use as solvent, unless stated otherwise, in the NMR experiments. Assignments are based on standard ^{1}H, ATP, ^{13}C high power decoupling (HPDEC) and 1D NOE-DIFF experiments. IR spectra were acquired on a 330 FT-IR instrument, using ATR technique.

Thionation of tryptanthrin (1), formation of 12b. Tryptanthrin **1** (248 mg, 1 mmol) was added to sulfolane (8 mL) at 110 °C followed b addition of the thionation reagent **7** (380 mg,

1mmol) at 110 °C. The reaction was completed by a period (10 min, 130 °C). The bluish-black reaction mixture was allowed to cool and then poured into water. The blackish product was purified from hot DMF, 190 mg (78%) of **12b**, mp >260 °C. IR 1622, 1600, 1486, 1455, 1347, 1154, 738 cm^{-1}. No NMR data could be obtained for this compound due to solubility reasons. Anal. Calcd. for $C_{30}H_{16}N_4S_2$: C, 72.50; H, 3.25; N, 11.28, Found: C, 72.15; H, 3.08; N, 10.97.

Thionation of the dimeric compound 12a. Compound **12a** (116 mg, 0.5 mmol) was added to sulfolane (6 mL) at 110 °C followed by addition of the thionation reagent **7** (380 mg, 1 mmol) at 110 °C. After a period (10 min, 130 °C) the bluish-black reaction mixture was poured into water. The blackish solid formed was purified from hot DMF, 108 mg, (78%) of **12b**, which was identical with the product obtained in the previous experiment.

6-Hydroxy-5a,6-dihydroindolo[2,1-b]quinazolin-12(5H)-one (8). This molecule was prepared as described in the literature,[26] yield 90 %. The spectroscopic properties were in agreement with data in the literature[26].

Indolo[2,1-b]quinazolin-12(6H)-one (10a). This molecule was prepared as described in the literature, yield (60 %)[26].

Indolo[2,1-b]quinazolin-12(6H)-thione (10b). Compound **8** (234 mg, 1 mmol) was added, under argon, to sulfolane (10 mL) at 100 °C followed by the reagent **7** (492 mg, 1 mmol). After 10 min the temperature was increased to 135 °C and this temperature kept for 20 min. The reaction mixture was allowed to cool and added to water. The solid formed was collected and then separated by column chromatography on silica gel using CH_2Cl_2 containing a slowly increasing percentage of MeOH which yielded **10b** (125 mg, 50 %, mp 190 °C dec.) and small amounts of **9b** (20 mg, 8 %, mp 190 °C dec.). However, **9b** seems to be a more stable form than **10b**. Tautomer **9b** gave the following data. ^{1}H NMR ($DMSO_{-d6}$): δ 6.03 (s, 1H), 7.15 (m, 2H),

7.25 (m, 2H), 7.54 (dd, 1H), 7.70 (dd, 1H), 8.16 (dd, 1H), 8.58 (d, 1H), 11.7 (s, 1H) ppm. ^{13}C NMR: δ 80.4, 111.1, 115.0, 115.3, 117.9, 119.5, 120.1, 124.1, 127.5, 129.1, 130.2, 134.8, 137.3, 140.4, 158.5. Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found: C, 72.08; H. 3.97; N, 11.05.

The major Tautomer **10b** gave the following data. ^{1}H NMR ($CDCl_3$): δ 4.08 (s, 2H), 7.34 (m, 1H), 7.45-7.55 (m, 3H), 7.74 (m, 1H), 7.79 (m. 1H), 8.50 (d, 1H), 8.62 (d, 1H). ^{13}C NMR: δ 35.9 (t), 96.2, 100.7, 117.4, 124.5, 126.3, 126.8, 126.9, 127.0, 128.5, 134.4, 140.1, 146.1, 160.1, 185.0.

2-(2-Acetylaminophenyl)benzothiazole (16).Ammonia (aq.,8.0 mL) was added to the purported bromination product of 2-methyl-3-phenylquinazoline-4(3H)-tione **14** (3.32 g, 0.01 mol)[32] in methanol (40 mL) and the reaction mixture was heated at reflux temperature for 1 h. Concentration and addition of water gave the benzothiazole derivative **16** (2.2 g, 88%), mp 120-121 °C. The spectroscopic data were in agreement with those in the literature. [33,34]

Synthesis of 13b-trifluoromethyl-13b,14-dihydrorutaecarpine (21). This compound was synthesized as previously described[40]. ^{1}H NMR δ 2.83 (m, 1H), 2.97 (m, 1H), 3.35 (m, 1H), 5.27 (m, 1H), 6.90 (dd, J_1=8.10 Hz, J_2=1.90 Hz), 6.94 (d, J=1.90 Hz), 7.12 (dd, 1H), 7.27 (dd, 1H), 7.59 (d, 1H, J=8.10 Hz), 7.81 (d, 1H), 8.10 (s, 1H), 11.0 (s, 1H); ^{13}C NMR: δ 19.8 (t), 37.4 (t), 70.6 (q, J_2=30.8 Hz), 112.4 (d), 112.5 (s), 113.6 (s), 113.9 (d), 119.0 (d), 119.5 (d), 123.2 (d), 124.2 (s), 124.9 (s), 125.6 (q, J_1=301.5 Hz), 129.7 (d), 137.0 (s), 138.3 (s), 145.0 (s), 160.7 (s).

Syntheis of 26 by thionation of 21. Compound **21** (288 mg, 1 mmol) was added to sulfolane (8mL) at 115 °C followed by addition of the thionation agent **7** (296 mg, 1 mmol). The reaction was completed at 160 °C (20 min). The pale-yellow reaction mixture was allowed to cool and

then poured into water. The solid formed was collected and recrystallized from ethanol-water to give compound **26** as a 1:1 complex with sulfolane, 301 mg (75%), mp 260 °C dec. IR 1611, 1483, 1165, 1142, 934, 758 cm^{-1}. ^{1}H NMR δ 2.88 (m, 1H), 3.05 (m, 1H), 3.69 (m, 1H), 6.44 (m, 1H), 6.89-6.94 (m, 2H), 7.13 (dd, 1H), 7.28 (dd, 1H), 7.41 (dd, 1H), 7.60-7.63 (m, 2H), 8.01 (s, 1H), 8.36 (d, 1H), 11.2 (s, 1H); ^{13}C NMR: δ 19.8 (t), 37.4 (t), 70.5 (q, J_2=30.5 Hz), 112.4 (d), 112.4 (s), 115.3 (d), 119.0 (d), 119.5 (d), 119.6 (d), 121.4 (s), 123.3 (d), 124.4 (s), 124.7 (q, J_1=290.5 Hz), 124.8 (s), 133.0)s), 134.0 (d), 137.1 (s), 139.0 (s), 191.5 (s).). Anal. Calcd. for $C_{19}H_{14}F_3N_3O$: C, 63.86; H, 3.95; N, 11.76. Found: C, 63.60; H, 3.79; N, 11.55.

Synthesis of 24 by thionation of rutaecarpine (22). Rutaecarpine (2.88 g, 0.01 mol) was added to sulfolane (35 mL at 100 °C), followed by addition of the thionation reagent **7** (2.96 g, 0.005 mol) at 100 °C. The reaction was completed by a period (20 min) at 135 °C. The yellow reaction mixture was allowed to cool whereupon water (150 mL) was added. The crude product was crystallized from HOAc-DMF, 1:1:1 to give **24** (2.21 g, 70%) mp >260 °C dec. IR 3430, 3030, 1619, 1592, 1561, 1302, 1215, 1146, 1105, 941, 740 cm^{-1}. ^{1}H NMR δ 3.23 (t, 2H), 5.08 (t, 2H), 7.08 (dd, 1H), 7.28 (dd, 1H), 7.50-7.53 (m, 2H), 7.64 (d, 1H), 7.71 (d, 1H), 7.84 (dd, 1H), 8.67 (d, 1H), 11.9 (s, 1H) cm^{-1}. ^{13}C NMR: δ 19.0 (t), 49.1 (t), 112.6 (d), 118.1 (s), 119.8 (d), 120.0 (d), 124.6 (s), 125.0 (d), 127.0 (s), 127.1 (d), 127.3 (d), 128.0 (s), 131.2 (d), 134.8 (d), 139.0 (s), 142.4 (s), 144.3 (s), 187.5 (s). Anal. Calcd. for $C_{18}H_{13}N_3S$: C, 71.26; H, 4.32; N, 13.85. Found: C, 71.06; H, 4.25;

N, 13.68.

7,8-Dehydrorutaecarpine (27*).* The method described before was used,[40] but on a 10-fold scale. DDQ (4.54, 0.02 mol) in dioxane (100 mL) was added to a solution of rutaecarpine (5.74 g, 0.02 mol) in dioxane (250 mL). After a period of reflux, 0.5 h, the reaction mixture was

evaporated and the residue extracted with a solution of KOH (15 g) in water (300 mL). The procedure was repeated until all DDQ-2H had been removed. The residue was recrystallized from DMF-ethanol, yield 4.95 g (80%), mp 280-281 °C, lit. mp 280-281 °C)[40]. IR 3232, 1673, 1635, 1570, 1540, 1505, 1463, 1331, 1245, 1158, 1147, 909, 764, 751, 730 cm^{-1}. ^{1}H NMR δ 7.25 (dd, 1H), 7.44-7.48 (m, 2H), 7.68 (d, 1H), 7.75 (d, 1H), 7.80 (d, 1H), 7.88 (dd, 1H), 8.10 (d, 1H), 8.31 (d, 1H), 8.57, (d, 1H), 12.6 (s, 1H). ^{13}C NMR δ 107.9 (d), 112.7 (d), 115.9 (s), 117.6 (d), 119.8 (s), 120.4 (d), 120.7 (d), 121.7 (s), 124.3 (d), 126.1 (d), 126.5 (d), 126.9 (d), 129.3 (s), 134.6 (d), 139.9 (s), 140.0 (s), 147.5 (s), 158.5 (s).

Synthesis the complex 28 by thionation of 7,8-Dehydrorutaecarpine (27*).* 7,8-Dehydro-rutaecarpine **27** (2.16 g, 0.01 mol) was added to sulfolane (35 mL) at 115 °C. The reaction was completed by a period (20 min) at 135 °C. The yellow-orange reaction mixture was allowed to cool, whereupon water (150 mL) was added. The crude product was crystallized from DMF-ethanol to give **28**, yield 2.55 g (75%), mp 260 °, dec. IR 1732, 1663, 1546, 1480, 1299, 1143, 1095, 906, 750 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.22 (dd, 1H), 7.39 (dd, 1H), 7.79 (d, 1H), 7.90 (d, 1H), 7.94 (dd, 1H), 8.00 (dd, 1H), 8.11 (dd, 1H), 8.13 (dd, 1H), 8.39 (d, 1H), 8.64 (d, 1H), 12.6 (s, 1H). No satisfactory analytical data could be obtained for this compound, which still contained some sulfolane.

Hydrolysis of compound 28. Compound **28** (379 mg, 1mmol) was heated at reflux temperature for 30 min in ethanol (20 mL) and water (10 mL) containing sodium hydroxide (100 mg). The clear solution was concentrated; water containing acetic acid (150 mg) was added. The solid of 7,8-dehydrorutaecarpine was collected, washed with water and dried, 204 mg (90%).

Synthesis of thionated dehydrorutaecarpine (30). 7,8-Dehydrorutaecarpine **27** (287 mg, 1 mmol) was added to sulfolane (8 mL) at 120 °C followed by the reagent **7** (984 mg, 2 mmol).

The temperature was increased to 165 °C for 20 min, whereupon the mixture was allowed to cool. After addition of water and collection by filtration the phosphorus-containing crude product was heated at reflux temperature for 30 min in ethanol (20 mL) and water (10 mL) containing sodium hydroxide (200 mg). The clear solution was concentrated; water containing acetic acid (150 mg) was added. The solid of **30**, was collected washed with water and dried, 210 mg (70%), mp 260 °C. ^{1}H NMR (DMSO-d_6): δ 6.98 (dd, 1H), 7.25 (dd, 1H), 7.50-7.55 (m, 2H), 7.66 (d, 1H), 7.74 (d, 1H), 7.99-8.04 (m, 2H), 8.17 (d, 1H), 8.37 (d, 1H). ^{13}C NMR (DMSO-d_6): δ 109.3 (d), 112.5 (d), 114.7 (s), 119.0 (d), 119.3 (d), 119.5 (d), 121.3 (d), 121.6 (s), 125.8 (s), 127.5 (d), 128.5 (s), 131.2 (d), 133.5 (d), 135.7 (d), 140.3 (s), 140.8 (s), 144.4 (s), 170.0 (s).). Anal. Calcd. for $C_{18}H_{11}N_3S$: C, 71.74; H, 3.68; N, 13.94. Found: C, 71.60; H, 3.58; N, 13.78.

Synthesis of 37. This compound was prepared using the method described for **31**. Yield: 85%, mp 210 °C dec. IR 3339, 2937, 1615, 1589, 1543, 1456, 1422, 1327, 1302, 1219, 1077, 940, 813 cm^{-1}. ^{1}H NMR δ 2.80 (m, 1H), 2.94 (m, 1H), 3.27 (m, 1H), 5.15 (dd, 1H), 6.90 (dd, 1H), 6.93 (d, 1H), 7.12 (dd, 1H), 7.26 (dd, 1H), 7.58 (s, 1H), 7.59 (d, 1H), 7.81 (d, 1H), 8.10 (s, 1H). ^{13}C NMR: δ 19.8 (q), 39.0 (q), 70.5 (q, J_2=30.9 Hz), 112.3 (d), 112.5 (s), 113.6 (s), 113.9 (d), 119.0 (d), 119.1 (d), 119.5 (d), 123.2 (s), 124.2 (s), 124.9 (s), 125.2 (q, J_1=301.5 Hz), 129.7 (d), 137.0 (s), 138.3 (s), 145.0 (s), 160.7 (s). Anal. Calcd. for $C_{19}H_{13}ClF_3N_3O$: C, 58.25; H, 3.37; N, 10.73. Found: C, 57.95; H, 3.28; N, 10.56.

Synthesis of 38 by thionation of 37. Compound (**37**) (50 mg, 0.13 mmol) was added to the mixture and was added to the mixture and the temperature was increased (160 °C). After 0.5h another portion of reagent 7 was added; this step was repeated two more times. A total of 2.6 eq. of reagent **7**was used. The reaction mixture was allowed to cool and then heated in water for 10 min. The solid (**38**) formed was collected by filtration as a yellow solid, 63 mg (86%, mp >260

°C. ^{1}H NMR: δ 3.29 (t, 2H), 5.08 (t, 2H), 7.12 (dd, 1H), 7.33 (dd, 1H), 7.51 (d, 1H, J_1=8.5 Hz, 7.56 (dd, 1H, J_1=8.5 Hz, J_2=2.0 Hz), 7.66 (d, 1H, J_2=2.0 Hz), 7.67 (d, 1H), 8.64 (d, 1H), 11.90 (s, 1H). ^{13}C NMR: δ 19.0 (t), 49.1 (t), 112.7 (d), 118.9 (s), 120.0 (d), 120.2 (d), 124.6 (s), 125.3 (d), 126.0 (d), 126.7 (s), 126.8 (s), 127.5 (d), 133.3 (d), 139.2 (s), 139.6 (s), 143.5 (s), 145.5 (s), 186.9 (s). Anal. Calcd. for $C_{18}H_{12}ClN_3S$: C, 64.00, H, 3.58, N, 12.44. Found: C, 63.80, H, 3.47, N, 12.31.

Synthesis of 41 by thionation of euxylophoricine–A, 39. Euxylophoricine–A, (327 mg, 1 mmol) was thionated under standard conditions, with the reagent **7** in sulfolane, (135 °C, 20 min.) after H_2O work-up, **41** was obtained as a yellow solid, 280 mg, (82%) mp dec. ~260 °C. IR 3324, 1621, 1503, 1269, 1173, 1131, 942, 749 cm^{-1}. ^{1}H NMR: δ 2.82 (m, 1H), 3.00 (m, 1H), 3.63 (m, 1H), 3.75 (q, 3H), 3.86 (q, 3H), 6.40 (s, 1H), 6.41 (m, 1H), 7.11 (dd, 1H), 7.26 (dd, 1H), 7.50-7.64 (m, 2H),

7.78 (s, 1H), 7.84 (s, 1H), 11.1 (s, 1H). ^{13}C NMR: δ 19.6 (t), 45.7 (t), 55.7 (q), 55.8 (q), 97.9 (d), 112.3 (d), 112.4 (s), 113.9 (s), 114.8 (d), 117.1 (s), 119.0 (d), 119.5 (d), 123.2 (d), 124.5 (s), 124.7 (s), 134.7 (s), 137.1 (s), 138.8 (s), 154.8 (s), 189.8 (s). Anal. Calcd. for $C_{20}H_{17}N_3O_2S$ (after drying): C, 66.10; H, 4.71; N, 11.56. Found: C, 65.94; H, 4.70; N, 11.52.

SUPPORTING INFORMATION. NMR spectra of the majority of the compounds prepared are featured.

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