Synthesis of the Thia-analog of Angustidine, Angustoline, Naucléfine and Naucletine

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Condensation of 1-methyl-3,4-dihydrobenzo[*b*]thieno[2,3-*c*]pyridine (**6**) with nicotinic acid in the presence of ynamine (**12**) gave 2-nicotinyl-1,2,3,4-tetrahydro-1-methylenebenzo[*b*]thieno-[2,3-c]pyridine (**13**). Photocyclization of the enamide (**13**) afforded thia-analog of naucléfine (**15**). Thia-analogs of angustidine (**19**), and nauclétine (**27**) were prepared similary through photocyclization of the enamides **18** and **26**, respectively. Reduction of **27** with sodium borohydride gave thia-analog of angustoline (**29**).

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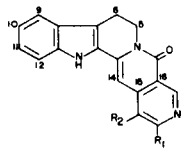
In 1973, Cheung and his workers isolated angustine (**1**), angustoline (**2**), and angustidine (**3**) from *Strychnos angustiflora* (1). Recently the related bases naucléfine (**4**) and nauclétine (**5**) were found in *Nauclea latifolia* (2). Their structures were assigned on the basis of spectral evidence and confirmed through the synthesis by us and others (3-6). It seemed worthwhile from a pharmacological point of view to investigate an effective synthesis of thia-analogs of angustidine, angustoline, naucléfine and nauclétine.



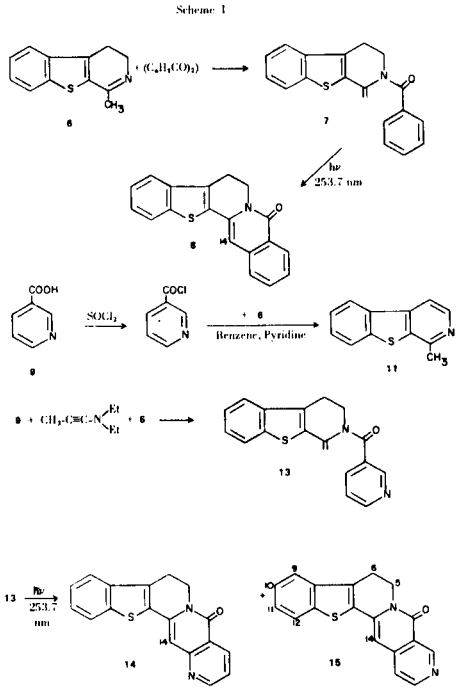
1. R_1 = H; R_2 = CH = CH_2
2. R_1 = H; R_2 = CH(OH) Me
3. R_1 = Me; R_2 = H
4. R_1 = R_2 = H
5. R_1 = H; R_2 = CO Me

The photocyclization reactions of enamides have been extensively studied during recent years and have proven to be very valuable for the synthesis of different type of alkaloids; namely, dehydroaporphines and aporphines (7), oxyprotoberberines (8), protoberberines and tetrahydroprotoberberines (9), benzophenanthridines (10) and 8-oxoberberines (11). We have recently investigated the possible application of photochemical reaction in benzo[*b*]thiophen moiety (12). In this work the synthesis of thia-analogs of naucléfine, angustidine, nauclétine and angustoline through the application of photocyclization reaction are described.

The feasibility of the photocyclization reaction was demonstrated as shown in Scheme I.

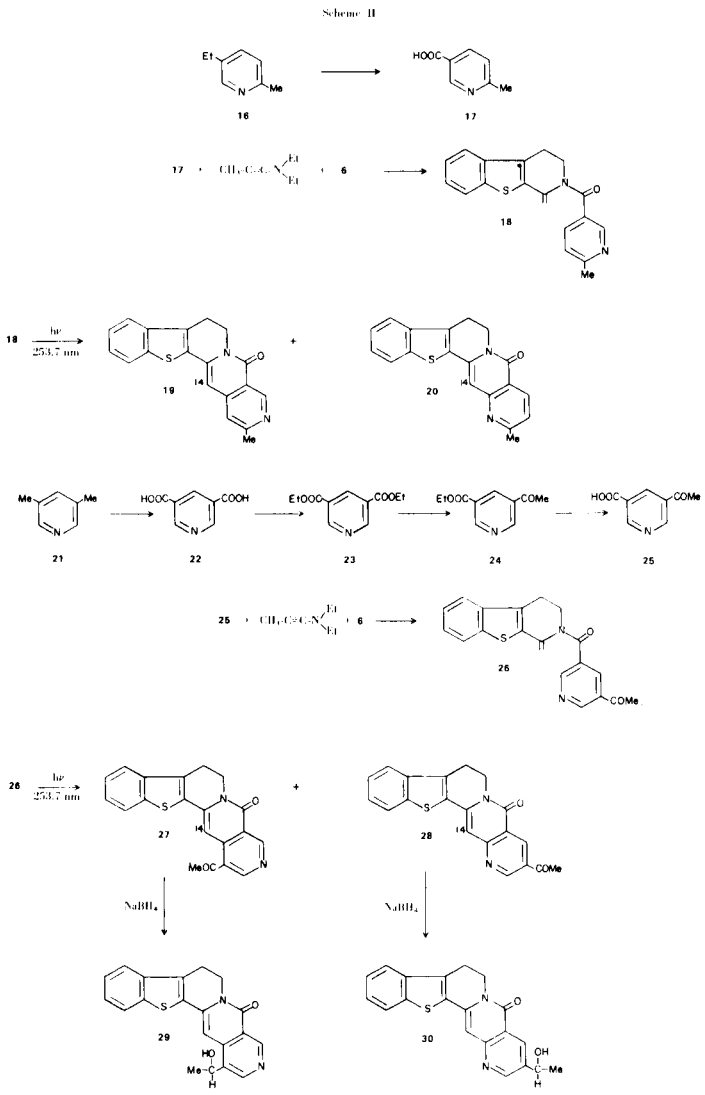
Benzoylation of 1-methyl-3,4-dihydrobenzo[*b*]thieno-[2,3-c]pyridine (**6**) (13) with benzoic anydride in benzene and pyridine afforded 2-benzoyl-1,2,3,4-tetrahydro-1-methylenebenzo[*b*]thieno[2,3-c]pyridine (**7**). Subsequent irradiation of the enamide **7** with low pressure mercury lamp gave in high yield the thia-analog of the oxoyohimbine derivative (**8**). This process was then applied for the synthesis of the thia-analog of naucléfine as it is shown in Scheme I.

Scheme I



The reaction of nicotinic acid (**9**) with thionyl chloride afforded the nicotinyl chloride (**10**), which without purification reacted with **6**; instead of the desired compound **13**, 1-methylbenzo[*b*]thieno[2,3-*c*]pyridine (**11**) (13) was isolated in 50% yield. The best method for the preparation of **13** was to perform the acid anydride of **9** in benzene using the ynamine (14), adding the compound **6** and refluxing. After usual work up, the enamide **13** was isolated in high yield. Irradiation of the enamide **13** for one hour gave in addition to the product **14** the thia-analog of naucléfine (**15**). These two compounds could be easily separated by tlc and differentiated by nmr. Compound **14** had only one α-pyridine proton appearing at 9.00 ppm as an unresolved quartet; while compound **15** had two α-pyridine protons, one appearing as a singlet at 9.60 and the other as a doublet at 8.69 ppm.

The thia-analog of angustidine (**19**) was prepared starting from **6** and 6-methylnicotinic acid (**17**) (15) as shown in Scheme II.



Irradiation of the enamide **18** gave in addition to thia-analog of angustidine (**19**), the side product **20**. The two products were separated by tlc. The nmr spectrum of compound **19** had one α-pyridine hydrogen which was deshielded by the amide group and appeared as a singlet at 9.53, while compound **20** had a γ pyridine proton which was also deshielded by the amide group and appeared as a doublet at 8.55 ppm.

The thia-analog of naucleïne (**27**) was prepared as it is shown in Scheme II. The required 3-acetyl-5-pyridine-carboxylic acid (**25**) was prepared starting from 3,5-lutidine (**21**). Oxydation of 3,5-lutidine with potassium permanganate afforded 3,5-pyridinedicarboxylic acid (**22**) in high yield. The desired compound **25** was obtained from diethyl 3,5-pyridinedicarboxylate (16) by a known method (17). The photocyclization of the enamide **26** gave in addition to the thia-analog of naucleïne (**27**), the side product **28**. In compound **27**, H_{14} is deshielded by the acetyl-carbonyl group and is appearing as a singlet at 8 ppm, while in compound **28**, H_{14} is appearing in its usual position at 7.12 ppm. Reduction of compound **27** with sodium borohydride afforded the thia-analog of angustoline (**29**), while the reduction of compound **28** afforded its isomer **30**.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Perkin-Elmer Model 267 spectrograph. Nmr spectra were determined using a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian MAT CH-5 spectrometer at 70eV. The compounds were irradiated with a 500 V low pressure mercury lamp at 253.7 nm.

2-Benzoyl-1,2,3,4-tetrahydro-1-methylenebenzo[*b*]thieno[2,3-*c*]-pyridine (**7**).

A solution of 100.5 mg. (0.5 mmole) of 1-methyl-3,4-dihydro-benzo[*b*]thieno[2,3-*c*]pyridine (**6**) (13) and 113 mg. (0.5 mmole) of benzoic anydride in 15 ml. of dry benzene and 1 ml. of pyridine was refluxed under nitrogen for 24 hours. The solvent was washed with water, dilute hydrochloric acid and water. The benzene was evaporated and the residue was crystallized from ether-hexane to give 105 mg. (69%) of **7**, m.p. 149-150°; nmr (deuteriochloroform): 7.8-7.21 (m, 9H, aromatic), 5.12 (d, 1H, ethylenic, J = 1.8 Hz), 4.59 (d, 1H, ethylenic, J = 1.8 Hz), 4.28 (t, 2H, CH_2), and 3.00 (t, 2H, CH_2) ppm; ir (potassium bromide): 1640 (amide) and 1620 cm^{-1} (ethylenic).

Anal. Calcd. for $C_{19}H_{15}NOS$: C, 74.75; H, 4.92; N, 4.59. Found: C, 74.93; H, 4.81; N, 4.39.

Irradiation of Benzoyl-1,2,3,4-tetrahydro-1-methylenebenzo[*b*]thieno[2,3-*c*]pyridine (**7**).

A solution of 101.7 mg. (0.33 mmole) of enamide **7** in 1 l. of benzene was irradiated for 90 minutes. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform/methanol: 96/4). The desired compound was crystallized from methanol to give 72%) of **8**, m.p. 168-170°; nmr (deuteriochloroform): 8.60-7.41 (m, 8H, aromatic), 6.77 (s, 1H, H_{14}), 4.56 (t, 2H, CH_2), and 3.13 (t, 2H, CH_2) ppm.

Anal. Calcd. for $C_{19}H_{13}NOS$: C, 75.24; H, 4.29; N, 4.62. Found: C, 75.06; H, 4.18; N, 4.49.

1-Methylbenzo[*b*]thieno[2,3-*c*]pyridine (**11**).

A solution of 201 mg. (1 mmole) of **6** and 1 mmole of nicotinyl chloride (prepared from 123 mg. (1 mmole) of nicotinic acid, 2 ml. of thionyl chloride and two drops of pyridine, refluxing for 10 minutes and evaporating to dryness) in 20 ml. of pyridine was refluxed for 1 hour. The solvent was evaporated. The sublimation of the residue gave 100 mg. (50%) of **11**, m.p. 108-109° [lit. 13, m.p. 110°]; nmr (deuteriochloroform): 8.70 (d, 1H, pyridine α-H), 8.50-7.40 (m, 5H, aromatic and pyridine β-H, and 2.85 (s, 3H, CH_3) ppm.

Anal. Calcd. for $C_{12}H_9NS$: C, 72.36; H, 4.52; N, 7.04. Found: C, 72.18; H, 4.45; N, 7.21.

2-Nicotinyl-1,2,3,4-tetrahydro-1-methylenebenzo[*b*]thieno[2,3-*c*]-pyridine (**13**).

To a suspension of 553.5 mg. (4.5 mmoles) of nicotinic acid (**9**) in 50 ml. of dry benzeve was added 166.5 mg. (1.5 mmoles) of *N,N*-diethylaminopropyne (**12**). The mixture was refluxed for 1.5 hours. To the mixture was added a solution of 301.5 mg. (15 mmoles) of **6** in 10 ml. of benzene and 1 ml. of pyridine. The mixture was refluxed under nitrogen for 24 hours. It was filtered and evaporated to dryness. The residue was crystallized

from methanol to give 295 mg. (71%) of **13**; m.p. 149-150°; nmr (deuteriochloroform): 8.81 (d, 1H, pyridine α-H), 8.69 (q, 1H, pyridine α-H), 7.89-7.13 (m, 6H, aromatic and pyridine β and γ protons), 5.15 (d, 1H, ethylenic, J = 1.8 Hz), 4.45 (d, 1H, ethylenic, J = 1.8 Hz), 4.24 (t, 2H, CH_2), and 3.02 (t, 2H, CH_2) ppm.

Anal. Calcd. for $C_{18}H_{14}N_2OS$: C, 70.59; H, 4.58; N, 9.15. Found: C, 70.41; H, 4.62; N, 9.01.

Irradiation of Nicotinyl-1,2,3,4-tetrahydro-1-methylenebenzo[*b*]-thieno[2,3-*c*]pyridine (**13**).

A solution of 306 mg. (1 mmole) of **13** in 1 l. benzene was irradiated for 45 minutes. The solvent was evaporated. The tlc of the residue (silica gel, chloroform/methanol; 97.5/2.5) gave two compounds. The fast moving fraction crystallized from ethanol to give 138 mg. (45%) of **14**. m.p. 194-196°; nmr (deuteriochloroform): 9.00 (q, 1H, pyridine γ-H), 8.73 (q, 1H, pyridine α-H), 8.0-7.20 (m, 5H, aromatic and pyridine β-H), 7.10 (s, 1H, H_{14}), 4.53 (t, 2H, CH_2), and 3.18 (t, 2H, CH_2) ppm; mass spectrum m/e 304 (M^+).

Anal. Calcd. for $C_{18}H_{12}N_2OS$: C, 71.05; H, 3.95; N, 9.21. Found: C, 71.21; H, 3.99; N, 9.02.

The slow moving fraction after crystallization from ethanol gave 72 mg. (24%) of thia-nauclefine (**15**); m.p. 234-235°; nmr (deuteriochloroform) 9.60 (s, 1H, pyridine α-H), 8.69 (d, 1H, pyridine α-H), 8.05-7.30 (m, 5H, aromatic and pyridine β-H), 6.70 (s, 1H, H_{14}), 4.61 (t, 2H, CH_2), and 3.20 (t, 2H, CH_2) ppm; mass spectrum m/e 304 (M^+).

Anal. Calcd. for $C_{18}N_{12}N_2OS$: C, 71.05; H, 3.95; N, 9.21. Found: C, 71.09; H, 3.98; N, 9.36.

2-(6-Methylnicotinyl)-1,2,3,4-tetrahydro-1-methylenebenzo[*b*]-thieno[2,3-*c*]pyridine (**18**).

This compound was prepared similar to **13** in 61% yield from 6-methylnicotinic acid (**17**) (15), diethylaminopropyne (**12**) and **6**, m.p. 147-148°; nmr (deuteriochloroform): 8.51 (d, 1H, pyridine α-H), 8.02-7.03 (m, 6H, aromatic and pyridine β, γ protons), 5.20 (d, 1H, ethylenic, J = 1.8 Hz), 4.50 (d, 1H, ethylenic, J = 1.8 Hz), 4.31 (t, 2H, CH_2), 3.07 (t, 2H, CH_2), and 2.58 (s, 3H, CH_3) ppm.

Anal. Calcd. for $C_{19}H_{16}N_2OS$: C, 71.25; H, 5.00; N, 8.75. Found: C, 71.38; H, 5.15; N, 8.56.

Irradiation of 2-(6-Methylnicotinyl)-1,2,3,4-tetrahydro-1-methylene-benzo[*b*]thieno[2,3-*c*]pyridine (**18**).

A solution of 320 mg. (1 mmole) of **18** in 1 l. benzene was irradiated for 75 minutes. The solvent was evaporated. The tlc of the residue (silica gel, chloroform/methanol; 97.5/2.5) gave two compounds. The fast moving fraction was crystallized from methanol to give 76 mg. (24%) of **20**, m.p. 252-253°; nmr (deuteriochloroform): 8.55 (d, 1H, pyridine γ-H), 8.0-7.10 (m, 5H, aromatic and pyridine β-H), 6.97 (s, 1H, H_{14}), 4.53 (t, 2H, CH_2), 3.15 (t, 2H, CH_2), and 2.68 (s, 3H, CH_3) ppm.

Anal. Calcd. for $C_{19}H_{14}N_2OS$: C, 71.70; H, 4.40; N, 8.81. Found: C, 71.85; H, 4.56; N, 8.94.

The slow moving fraction after crystallization from methanol gave 79 mg. of thia-analog of angustidine (**19**), m.p. 229-230°; nmr (deuteriochloroform): 9.53 (s, 1H, pyridine α-H), 8.03-7.34 (m, 4H, aromatic), 7.23 (s, 1H, pyridine β-H), 6.80 (s, 1H, H_{14}), 4.53 (t, 2H, CH_2), 3.21 (t, 2H, CH_2), and 2.68 (s, 3H, CH_3) ppm; ms: m/e 318 (M^+).

Anal. Calcd. for $C_{19}H_{14}N_2OS$: C, 71.70; H, 4.40; N, 8.81. Found: C, 71.65; H, 4.32; N, 8.75.

Pyridine 3,5-Dicarboxylic Acid (**22**).

To a stirring suspension of 35.5 g. (0.033 mole) of 3,5-dimethylpyridine (**21**) in 1 l. water 296 g. potassium permanganate was added in three equal portions in 24 hours. During this time the reaction mixture was gently refluxed. It was filtered and concentrated up to 200 ml. The solution was acidified with concentrated hydrochloric acid up to *p*H 1.5-2.5, and left in refrigrator overnight. The precipitate was filtered to give 32 g. (58%) of **22**, m.p. 320-321° [lit. 18, m.p. 322°].

Anal. Calcd. for $C_7H_5NO_4$: C, 50.53; H, 2.99; N, 8.38. Found: C, 50.45; H, 2.82; N, 8.27.

2-(5-Acetylnicotinyl)-1,2,3,4-tetrahydro-1-methylenebenzo[*b*]-thieno[2,3-*c*]pyridine (**26**).

This compound was prepared similar to **13** in 52% yield from 5-acetylnicotinic acid (**25**) (17), diethylaminopropyne (**12**) and **6**; m.p. 162-163°; nmr (deuteriochloroform): 9.13 (unresolved t, 1H, pyridine α-H, J = 2 Hz), 8.84 (unresolved t, 1H, pyridine α-H), 8.32 (unresolved t, 1H, pyridine γ-H), 7.98-7.22 (m, 4H, aromatic), 5.17 (d, 1H, ethylenic, J = 1.8 Hz), 4.41 (d, 1H, ethylenic, J = 1.8 Hz), 4.28 (t, 2H, CH_2), 3.07 (t, 2H, CH_2), and 2.61 (s, 3H, CH_3) ppm.

Anal. Calcd. for $C_{20}H_{16}N_2O_2S$: C, 68.97; H, 4.60; N, 8.05. Found: C, 68.82; H, 4.71; N, 8.15.

Irradiation of 2(5-Acetylnicotinyl)-1,2,3,4-tetrahydro-1-methylene-benzo[*b*]thieno[2,3-*c*]pyridine (**26**).

A solution of 348 mg. (1 mmole) of **26** in 1 l. benzene was irradiated for 90 minutes. The solvent was evaporated. The tlc of the residue (silica gel, chloroform/methanol; 92.5/7.5) gave two products. The fast moving fraction was crystallized from methanol-chloroform to give 114 mg. (33%) of **28**; m.p. 318-320°; nmr (deuteriochloroform): 9.45 (d, 1H, pyridine α-H, J = 2 Hz), 9.12 (d, 1H, pyridine γ-H, J = 2 Hz), 8.03-7.30 (m, 4H, aromatic), 7.12 (s, 1H, H_{14}), 4.10 (t, 2H, CH_2), 3.27 (t, 2H, CH_2), and 2.71 (s, 3H, CH_3) ppm.

Anal. Calcd. for $C_{20}H_{14}N_2OS$: C, 69.36; H, 4.05; N, 8.09. Found: C, 69.23; H, 4.21; N, 8.12.

The slow moving fraction after crystallization from methanol-chloroform gave 119 mg. (34%) of thia-analog of nauclétine (**27**); m.p. 299-300°; nmr (deuteriochloroform): 9.68 (d, 1H, pyridine α-H), 9.15 (d, 1H, pyridine α-H), 8.0 (s, 1H, H_{14}), 7.95-7.19 (m, 4H, aromatic), 4.11 (t, 2H, CH_2), 3.17 (t, 2H, CH_2), and 2.70 (s, 3H, CH_3) ppm.

Anal. Calcd. for $C_{20}H_{14}N_2OS$: C, 69.36; H, 4.05; N, 8.09. Found: C, 69.45; H, 4.16; N, 7.99.

Thia-analog of Angustoline (**29**).

To a stirring solution of 34.6 mg. (0.1 mmole) of **27** in 80 ml. ethanol was added 50 mg. sodium borohydride. After 30 minutes, water (100 ml.) was added and the product was extracted with chloroform, the solvent was evaporated and the residue was crystallized from methanol-chloroform to give 26.3 mg. of **29**; m.p. 253-254°; nmr (deuteriochloroform-trifluoroacetic acid): 9.52 (s, 1H, pyridine α-H), 8.98 (s, 1H, pyridine α-H), 8.10-7.44 (m, 4H, aromatic), 7.07 (s, 1H, H_{14}), 5.52 (q, 1H, HCO, J = 6 Hz), 4.69 (t, 2H, CH_2), 3.37 (t, 2H, CH_2), and 1.75 (d, 3H, CH_3, J = 6 Hz) ppm.

Anal. Calcd. for $C_{20}H_{16}N_2O_2S$: C, 68.97; H, 4.60; N, 8.05. Found: C, 68.81; H, 4.50; N, 8.22.

Thia-analog of *iso*-Angustoline (**30**).

This compound was prepared from **28** similar to **29** in 73% yield; m.p. 242-243° chloroform/methanol; nmr (deuteriochloroform-trifluoroacetic acid): 9.48 (d, 1H, pyridine α-H, J = 2 Hz), 9.15 (d, 1H, pyridine α-H, J = 2 Hz), 8.13-7.52 (m, 4H, aromatic), 7.16 (s, 1H, H_{14}), 5.40 (q, 1H, HCO, J = 6 Hz), 4.74 (t, 2H, CH_2), 3.42 (t, 2H, CH_2), and 1.78 (d, 3H, CH_3, J = 6 Hz) ppm.

Anal. Calcd. for $C_{20}H_{16}N_2O_2S$: C, 68.97; H, 4.60; N, 8.05.

Found: C, 68.99; H, 4.75; N, 8.18.

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