

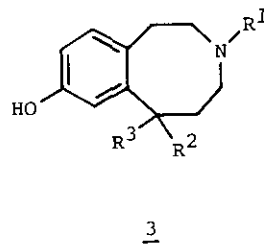
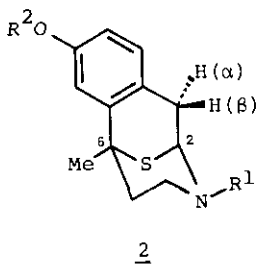
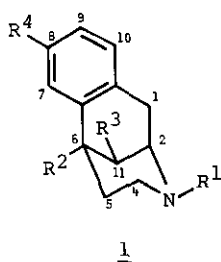
SYNTHESIS OF 1,2,3,4,5,6-HEXAHYDRO-8-HYDROXY-2,6-EPITHIO-3-BENZAZOCINE

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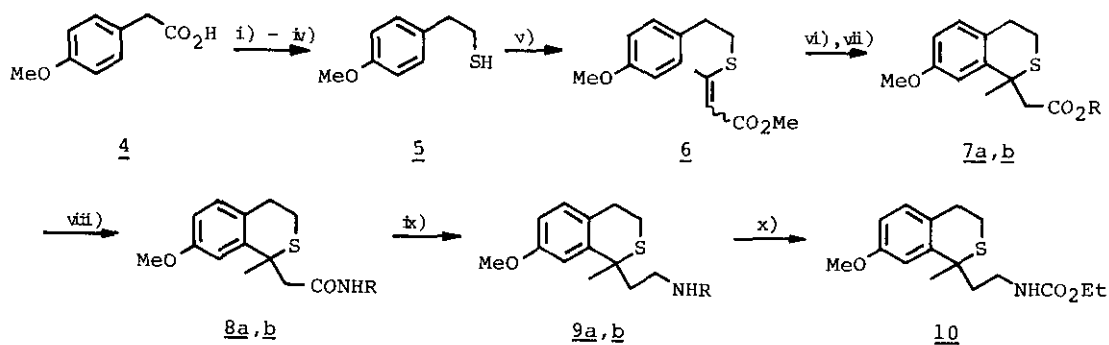
Abstract — In anticipation of diminishing narcotism of 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-3-benzazocine opioids, the corresponding 2,6-epithio-3-benzazocines (**2**) have been synthesized by intramolecular cyclization of 1-(2-aminoethyl)-3,4-dihydro-1H-2-benzothioopyrans (**9**) with tert-butyl hypochlorite, and subsequent treatment of the 5-membered cyclic aminosulfonium salts (**17**) with NaOH.

1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocines (6,7-benzomorphans, **1**) have been well-known to have the strong analgesic activities.¹ However, 3-benzazocines (**3**), in which the methano bridge of **1** is removed, did not show any analgesic activity in humans.² On the other hand, since the sulfide bonds are oxidatively metabolized with the C-S bond cleavage by P-450,³ 2,6-epithio-3-benzazocines (**2**) would be metabolized to 3-benzazocines (**3**). With these points as background, we designed 1,2,3,4,5,6-hexahydro-2,6-epithio-3-benzazocines (**2**) as candidates for strong analgesics with diminished narcotism. The epithiobenzazocines (**2**) would act as analgesics and then be metabolized to non-analgesic and non-narcotic compounds (**3**). This report describes the novel synthesis of 2,6-epithio-3-benzazocines.



p-Methoxyphenylacetic acid (**4**) was reduced with BH_3 in THF quantitatively to af-

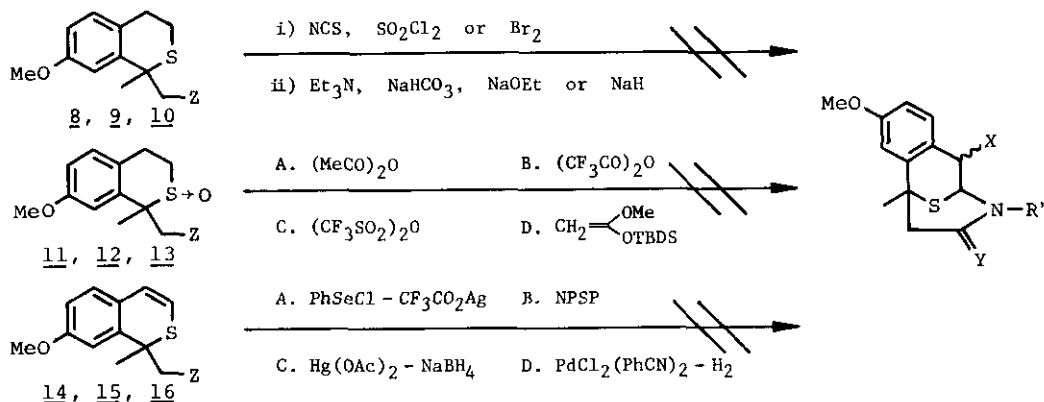
ford a phenethyl alcohol. The alcohol reacted with phosphorus tribromide to give a phenethyl bromide (95.2%), then the bromide was converted into the corresponding thiol (**5**) in 96.4% yield by the reaction with thiourea and subsequent alkaline hydrolysis. The thiol (**5**) was, immediately, condensed with methyl acetoacetate in the presence of *p*-toluenesulfonic acid to give a vinyl sulfide (**6**; 95.2%). The Friedel-Crafts type cyclization of **6** was attempted under various acidic conditions. The cyclization of **6** did not occur by the treatment with AlCl_3 , conc. sulfuric acid or trifluoroacetic acid. However, upon stirring in methanesulfonic acid, the vinyl sulfide (**6**) afforded a mixture of 3,4-dihydro-1H-2-benzothiopyrans (isothiochromans, **7a** and **7b**). The crude mixture was hydrolyzed with NaOH to give **7a** in 78.8% yield from **6**. Trifluoromethanesulfonic acid was also useful (68%), but neither BF_3 etherate nor 80% perchloric acid was so effective.



a : R = H, **b** : R = Me

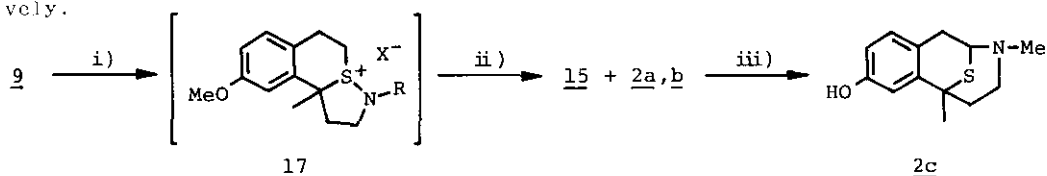
i) BH_3/THF , rt. ii) PBr_3/PhH , reflux. iii) $(\text{NH}_2)_2\text{CS}/\text{EtOH}$, reflux. iv) 3N-NaOH , reflux.
 v) $\text{MeCOCH}_2\text{CO}_2\text{Me}$, *p*-TsOH/PhH, reflux. vi) MeSO_3H , rt. vii) 3N-NaOH , reflux. viii) Et_3N , ClCO_2Et , $\text{RNH}_2/\text{CH}_2\text{Cl}_2$, -10°C . ix) BH_3/THF , reflux. x) ClCO_2Et , $\text{NaHCO}_3/\text{PhH}$, reflux.

The isothiochroman-1-acetic acid (**7a**) reacted with ethyl chloroformate in the presence of triethylamine and subsequent treatment with conc. NH_4OH or with methylamine solution, affording the corresponding acetamide (**8a** or **8b**) quantitatively. The acetamides (**8**) were reduced to amines (**9**) with BH_3 (**9a**; 81.5%, **9b**; 68.0%). The primary amine (**9a**) reacted with ethyl chloroformate to yield a urethane derivative (**10**) quantitatively. Compounds (**8**, **9** and **10**) were converted into the corresponding sulfoxides (**11**, **12** and **13**; 57.9-100%), or isothiochromenes (**14**, **15** and **16**; 58.5-82.0%), respectively. We have failed the cyclization of these sulfides, sulfoxides and isothiochromenes into 2,6-epithio-3-benzazocines by either the Bartrop-May's oxobenzomorphan synthesis,^{1,4} the Pummerer type reactions⁵ or even aminometallation. However, the amine (**9a** or **9b**) yielded the desired 2,6-epithio-3-benzazocine (**2a** or **2b**) in 26.6% or 16.3% yield, respectively, together with iso-



8, 11, 14: $\text{Z}=\text{CONHR}$. **9, 12, 15:** $\text{Z}=\text{CH}_2\text{NHR}$. **10, 13, 16:** $\text{Z}=\text{CH}_2\text{NHCO}_2\text{Et}$.
 NCS= $\bar{\text{N}}$ -chlorosuccinimide. TBDS= $\bar{\text{t}}$ -butyldimethylsilyl. NPSP= $\bar{\text{N}}$ -phenylselenophthalimide.

thiochromenes by treatment with tert-butyl hypochlorite in CH_2Cl_2 , and subsequent reaction with NaOH solution. Surprisingly, compounds (**2a, b**) are soluble in water as equally or much more than in CH_2Cl_2 or CHCl_3 , and consequently, the isolation yields of **2a, b** were low. However, we have succeeded in the isolation of the reaction intermediate, 5-membered cyclic aminosulfonium salt (**17**, $\text{R}=\text{H}$, $\text{X}=\text{BF}_4$) as semisolid, and upon treatment of the aminosulfonium salt (**17**) with NaOH, 2,6-epithio-3-benzazocine (**2a**) was obtained. Deprotonation was examined using some other bases, and KOH was also useful but n-butyllithium, sodium hydride and triethylamine were not. The secondary amino group of **2a** did not react with methyl iodide or ethyl chloroformate in the presence of NaHCO_3 in CHCl_3 . Demethylation of the 8-methoxy group of **2b** with BF_3 afforded the 8-hydroxy derivative (**2c**) quantitatively.



i) $\bar{\text{t}}\text{-BuOCl}/\text{CH}_2\text{Cl}_2$, $-75^\circ\text{C} \rightarrow \text{rt}$. ii) NaOH-aq , $0^\circ\text{C} \rightarrow \text{rt}$. iii) $\text{BBr}_3/\text{CH}_2\text{Cl}_2$, $0^\circ\text{C} \rightarrow \text{rt}$.

The structures of **2** were determined by ^1H - and ^{13}C -nmr spectra, mass spectra and high resolution mass spectra.⁶ The ^{13}C -nmr spectrum of **2a**, **2b** or **2c** showed the methine signal of the C(2) carbon at δ 54.8, 63.0 or 62.7, respectively. In ^1H -nmr spectra, the modes of each spin-spin coupling of adjacent protons of **2** were similar to those of a known 2,6-methano-3-benzazocine (**1**; $\text{R}^1=\text{R}^2=\text{R}^3=\text{Me}$, $\text{R}^4=\text{H}$) and, as a result, the conformation of **2** was confirmed.

Evaluation of the pharmacological activity of **2c** is now in progress.

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6. **2a**: Pale yellow oil. $\text{Ir}(\text{Film})\text{cm}^{-1}$: 3300(NH). $^1\text{H Nmr}(\text{CDCl}_3)\delta$: 1.51(1H, ddd, J= 2.5, 3, 13 Hz, e-C⁵-H), 1.67(3H, s, C⁶-CH₃), 1.82(1H, ddd, J=4.5, 12.5, 13 Hz, a C⁵-H), 2.86(1H, ddd, J 3, 12.5, 14 Hz, a C¹-H), 2.99(1H, ddd, J 2.5, 4.5, 14 Hz, e C⁵-H), 3.17(1H, d, J 17.5 Hz, β -C¹-H), 3.52(1H, dd, J= 6.5, 17.5 Hz, α -C¹-H), 3.79(3H, s, OCH₃), 4.59(1H, d, J=6.5 Hz, C²-H), 6.74(1H, dd, J=2.5, 8.5 Hz, C³-H), 6.84(1H, d, J=2.5 Hz, C⁷-H), 7.06(1H, d, J 8.5 Hz, C¹⁰-H). $^{13}\text{C Nmr}(\text{CDCl}_3)\delta$: 28.8(C⁶-CH₃), 37.2(C⁵), 39.7(C¹), 40.6(C⁹), 41.6(C¹), 54.8(C³), 55.1(OCH₃), 109.4(C⁹), 111.2(C⁷), 129.1(C¹⁰), 129.3(C¹⁰), 142.5(C⁹), 157.4(C⁸). High ms calcd for C₁₃H₁₇N₂O₂S(M⁺): 235.10307. Found: 235.10248.
- 2b**: Pale yellow oil. $^1\text{H-Nmr}(\text{CDCl}_3)\delta$: 1.09-1.15(1H, m, e C⁵-H), 1.66(3H, s, C⁶-CH₃), 2.08-2.19(1H, m, a C⁵-H), 2.60-2.65(1H, m, e C¹-H), 2.63(3H, s, NCH₃), 2.97-3.08(1H, m, a C¹-H), 3.23(1H, d, J 17.5 Hz, β -C¹-H), 3.56(1H, dd, J=6.5, 17.5 Hz, α -C¹-H), 3.79(3H, s, OCH₃), 4.23(1H, d, J 6.5 Hz, C²-H), 6.74(1H, dd, J= 2.5, 8.5 Hz, C³-H), 6.80(1H, d, J=2.5 Hz, C⁷-H), 7.06(1H, d, J 8.5 Hz, C¹⁰-H). $^{13}\text{C-Nmr}(\text{CDCl}_3)\delta$: 28.8(C⁶-CH₃), 34.1(C⁵), 37.6(C¹), 41.0(C⁹), 41.6(NCH₃), 46.2(C¹), 55.3(OCH₃), 63.0(C³), 109.4(C⁹), 111.4(C⁷), 129.0(C¹⁰), 129.5(C¹⁰), 142.4(C⁹), 157.6(C⁸). Ms(m/z): 249(M⁺).
- 2c**: Colorless needles, mp 192-193°C(CH₂Cl₂-acetone). Anal. calcd for C₁₃H₁₇NOS: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.07; H, 7.29; N, 5.86. $\text{Ir}(\text{KBr})\text{cm}^{-1}$: 3400(OH). $^1\text{H Nmr}(\text{CDCl}_3)\delta$: 1.16(1H, br d, J 14 Hz, e-C⁵-H), 1.63(3H, s, C⁶-CH₃), 2.15(1H, ddd, J=4, 13, 13 Hz, a C⁵-H), 2.63-2.67(1H, m, e C¹-H), 2.66(3H, s, NCH₃), 3.04(1H, ddd, J=3.5, 13, 13.5 Hz, a C¹-H), 3.25(1H, d, J=17.5 Hz, α -C¹-H), 3.54(1H, dd, J=7, 17.5 Hz, β -C¹-H), 4.23(1H, d, J 7 Hz, C²-H), 6.65(1H, dd, J=2.5, 8 Hz, C³-H), 6.74(1H, d, J=2.5 Hz, C⁷-H), 6.97(1H, d, J 8 Hz, C¹⁰-H). $^{13}\text{C Nmr}(\text{CDCl}_3)\delta$: 28.5(C⁶-CH₃), 34.2(C⁵), 37.1(C¹), 40.8(C⁹), 41.4(NCH₃), 46.1(C¹), 62.7(C³), 110.1(C⁹), 113.9(C⁷), 128.3(C¹⁰), 129.7(C¹⁰), 142.3(C⁹), 153.9(C⁸). Ms(m/z): 235(M⁺).

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