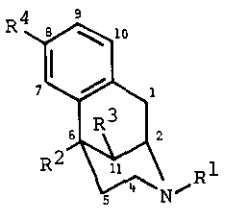
SYNTHESIS OF 1,2,3,4,5,6-HEXAHYDRO-8-HYDROXY-2,6-EPITHIO-3-BENZAZOCINE

Mikio Hori,*,[a] Hiroyuki Ozeki,[a] Tatsunori Iwamura,[a] Hiroshi Shimizu,[a] Tadashi Kataoka,[a] and Noriyuki Iwata[b]

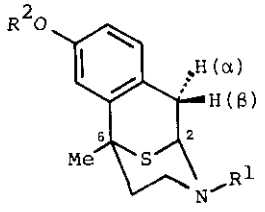
Gifu Pharmaceutical University,[a] 5-6-1 Mitahora-higashi, Gifu 502 Japan and Nagoya Laboratory, Sanwa Kagaku Kenkyusho Ltd.,[b] 1212 Gejo-cho, Kasugai, Aichi 486 Japan

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-1*H*-2-benzothiopyrans (**9**) with tert-butyl hypochlorite, and subsequent treatment of the 5-membered cyclic aminosulfonium salts (**17**) with NaOH.

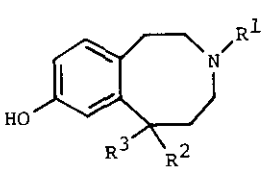
1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocines (6,7-benzomorphans, **1**) have been well-known to have the strong analgesic activities.[1] However, 3-benzazocines (**3**), in which the methano bridge of **1** is removed, did not show any analgesic activity *in humans*.[2] On the other hand, since the 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.



1



2

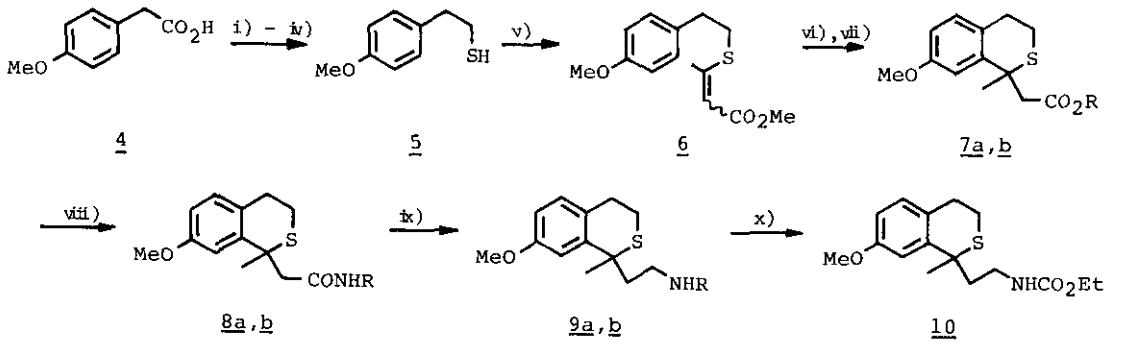


3

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%).

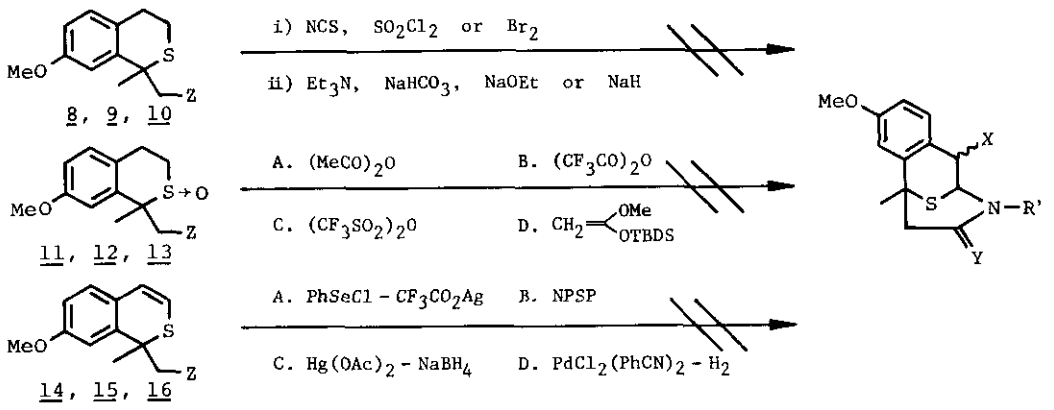
The Friedel-Crafts type cyclization of 6 was attempted under various acidic conditions. The cyclization of 6 did not occur by the treatment with $AlCl_3$, conc. sulfuric acid or trifluoroacetic acid. However, upon stirring in methanesulfonic acid, the vinyl sulfide (6) afforded a mixture of 3,4-dihydro-1H-2-benzothiopyrans (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

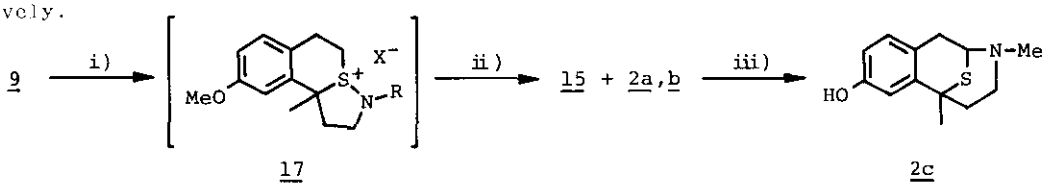
i) BH_3/THF, rt. ii) PBr_3/PhH, reflux. iii) $(NH_2)_2CS$/EtOH, reflux. iv) 3N-NaOH, reflux. v) $MeCOCH_2CO_2Me$, p-TsOH/PhH, reflux. vi) $MeSO_3H$, rt. vii) 3N-NaOH, reflux. viii) Et_3N, $ClCO_2Et$, RNH_2/CH_2Cl_2, -10℃. ix) BH_3/THF, reflux. x) $ClCO_2Et$, $NaHCO_3$/PhH, reflux.

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 Barltrop-May's oxobenzomorphan synthesis,[1,4] the Pummerer type reactions[5] 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: Z=CONHR. 9, 12, 15: Z=CH_2NHR. 10, 13, 16: Z=CH_2NHCO_2Et.
NCS=N-chlorosuccinimide. TBDS=t-butyldimethylsilyl. NPSP=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, R=H, X=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) t-BuOCl/CH_2Cl_2, -75℃→rt. ii) NaOH-aq, 0℃→rt. iii) BBr_3/CH_2Cl_2, 0℃→rt.

The structures of 2 were determined by ^{1}H- 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 ^{1}H-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; R^1=R^2=R^3=Me, R^4=H) and, as a result, the conformation of 2 was confirmed.

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

REFERENCES AND NOTES

1. D.C. Palmer and M.J. Strauss, Chem. Rev., 1977, **77**, 1.

2. Y. Sawa, T. Kato, A. Morimoto, T. Masuda, M. Hori, and H. Fujimura, Yakugaku Zasshi, 1975, **95**, 261.

3. S. Oae, A. Mikami, T. Matuura, K. Ogawa-Asada, Y. Watanabe, K. Fujimori, and T. Iyanagi, Biochem. Biophys. Res. Commun., 1985, **131**, 567; S. Oae, K. Asada, and T. Yoshimura, Tetrahedron Lett., 1983, **24**, 1265; Y. Watanabe, S. Oae, and T. Iyanagi, Bull. Chem. Soc. Jpn., 1982, **55**, 188; Y. Watanabe, T. Numata, T. Iyanagi, and S. Oae, ibid., 1981, **54**, 1163.

4. J.A. Barltrop, J. Chem. Soc., 1947, 399; J.G. Murphy, J.H. Ager, and E.L. May, J. Org. Chem., 1960, **25**, 1386.

5. M. Hori, T. Kataoka, H. Shimizu, E. Imai, N. Iwata, N. Kawamura, and M. Kurono, Heterocycles, 1988, **27**, 2091; Y. Kita, O. Tamura, T. Miki, and Y. Tamura, Tetrahedron Lett., 1987, **28**, 6479; Y. Kita, J. Segawa, H. Haruta, H. Yasuda, and Y. Tamura, J. Chem. Soc. Perkin Trans. 1, 1982, 1099.

6. **2a**: Pale yellow oil. Ir(film)cm^{-1}:3300(NH). ^{1}H Nmr($CDCl_3$)δ:1.51(1H, ddd, J= 2.5, 3, 13 Hz, e-C^5 H), 1.67(3H, s, C^6-CH_3), 1.82(1H, ddd, J=4.5, 12.5, 13 Hz, a C^5-H), 2.86(1H, ddd, J 3, 12.5, 14 Hz, a-C^4-H), 2.99(1H, ddd, J 2.5, 4.5, 14 Hz, e C^5 H), 3.17(1H, d, J 17.5 Hz, β-C^1-H), 3.52(1H, dd, J=6.5, 17.5 Hz, α C^1-H), 3.79(3H, s, OCH_3), 4.59(1H, d, J=6.5 Hz, C^2 H), 6.74(1H, dd, J=2.5, 8.5 Hz, C^9-H), 6.84(1H, d, J=2.5 Hz, C^7-H), 7.66(1H, d, J 8.5 Hz, C^{10} H). ^{13}C Nmr($CDCl_3$)δ: 28.8(C^6-CH_3), 37.2(C^5), 39.7(C^4), 40.6(C^6), 41.6(C^1), 54.8(C^2), 55.1(OCH_3), 109.4(C^9), 111.2(C^7), 129.1(C^{10a}), 129.3(C^{10}), 142.5(C^5), 157.4(C^8). High ms calcd for $C_{13}H_{17}NO_2S$(M^+): 235.10307. Found: 235.10248.

2b: Pale yellow oil. ^{1}H-Nmr($CDCl_3$)δ:1.09-1.15(1H, m, e C^5 H), 1.66(3H, s, C^6 CH_3), 2.08-2.19(1H, m, a C^5 H), 2.60-2.65(1H, m, e C^4 H), 2.63(3H, s, NCH_3), 2.97-3.08(1H, m, a-C^4 H), 3.23(1H, d, J 17.5 Hz, β C^1-H), 3.56(1H, dd, J=6.5, 17.5 Hz, α C^1-H), 3.79(3H, s, OCH_3), 4.23(1H, d, J=6.5 Hz, C^2 H), 6.74(1H, dd, J= 2.5, 8.5 Hz, C^9 H), 6.80(1H, d, J=2.5 Hz, C^7-H), 7.06(1H, d, J 8.5 Hz, C^{10}-H). ^{13}C-Nmr($CDCl_3$)δ: 28.8(C^6-CH_3), 34.1(C^5), 37.6(C^4), 41.0(C^6), 41.6(NCH_3), 46.2(C^1), 55.3(OCH_3), 63.0(C^2), 109.4(C^9), 111.4(C^7), 129.0(C^{10a}), 129.5(C^{10}), 142.4(C^{5a}), 157.6(C^8). Ms(m/z): 249(M^+).

2c: Colorless needles, mp 192-193℃(CH_2Cl_2-acetone). Anal. calcd for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.07; H, 7.29; N, 5.86. Ir(KBr)cm^{-1}: 3400(OH). ^{1}H Nmr($CDCl_3$)δ:1.16(1H, br d, J 14 Hz, e-C^5-H), 1.63(3H, s, C^6-CH_3), 2.15(1H, ddd, J=4,13,13 Hz, a C^5-H), 2.63-2.67(1H, m, e C^4-H), 2.66(3H, s, NCH_3), 3.04(1H, ddd, J=3.5, 13, 13.5 Hz, a C^4 H), 3.25(1H, d, J=17.5 Hz, α-C^1-H), 3.54(1H, dd, J=7, 17.5 Hz, β C^1-H), 4.23(1H, d, J 7 Hz, C^2-H), 6.65(1H, dd, J=2.5, 8 Hz, C^9-H), 6.74(1H, d, J=2.5 Hz, C^7 H), 6.97(1H, d, J 8 Hz, C^{10} H). ^{13}C Nmr($CDCl_3$)δ: 28.5(C^6 CH_3), 34.2(C^5), 37.1(C^4), 40.8(C^6), 41.4(NCH_3), 46.1(C^1), 62.7(C^2), 110.1(C^9), 113.9(C^7), 128.3(C^{10a}), 129.7(C^{10}), 142.3(C^{5a}), 153.9(C^8). Ms(m/z): 235(M^+).

Received, 14th October, 1989