A FACILE SYNTHESIS OF 4-MERCAPTOINDOLES

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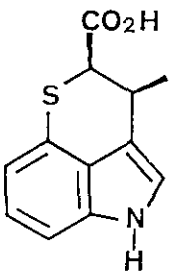
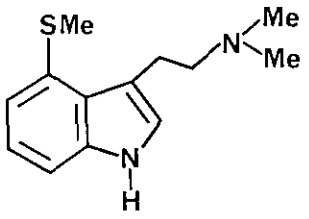
Abstract——4-(Ethoxythiocarbonylthio)-1-(p-toluenesulfonyl)indole was synthesized and used as a stable equivalent of 4-mercaptoindoles.

Indole with a mercapto group at the 4-position constructs the skeleton of chuangxinmycin and N,N-dimethyl-4-methylthiotryptamine. The former is unique antibiotic isolated recently from a strain of Actinoplanes jinanensis n. sp.[1] and synthesized by two research groups.[2] The latter has also been synthesized and evaluated as a hallucinogen.[3] 4-Mercaptoindoles have, however, been rather difficult of access so far.[4-6] We wish to describe here a facile synthesis of 4-mercaptoindoles by the use of 4-(ethoxythiocarbonylthio)-1-(p-toluenesulfonyl)indole (2) as a stable precursor.[5,6]

The xanthate 2 was synthesized from 1-(p-toluenesulfonyl)-4-indolediazonium tetrafluoroborate (1),[7] which was easily prepared as stable crystals from 5-



1
Chuangxinmycin

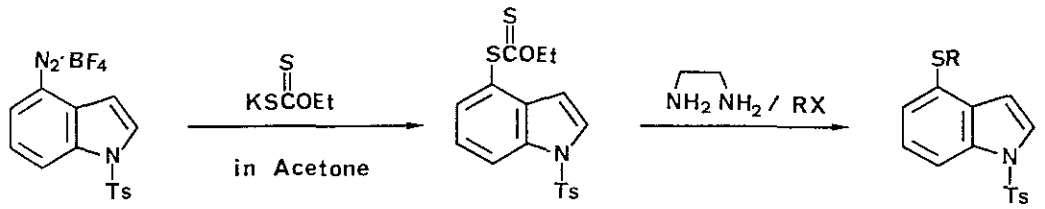


N,N-Dimethyl-4-methylthiotryptamine

chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole through 4-amino-1-(p-toluenesulfonyl)indole.[8] When the diazonium salt 1 was added to a solution of potassium ethyl xanthate (KSCSOEt) in acetone at room temperature, the indole 2[9] was produced in 86% yield.

Transformation of the xanthate 2 into 4-mercaptoindoles 3 was effected by ethylenediamine(EDA).[10] Treatment of 2 (0.52mmol) in EDA (0.5mL) at 30 °C for 16.5h gave S-free indole 3a(R=H) in 94% yield.[11] The mercaptan 3a was rather unstable to air to give the corresponding disulfide.

Addition of halides to the above reaction system led to S-substituted 4-mercaptoindoles 3. When ethyl chloroacetate (3.0 mL) was added to a solution of the indole 2 (12.9 mmol) and EDA (3.0mL) in dry THF (35mL) and stirred at room temperature for 1 h, 4-(ethoxycarbonylmethylthio)-1-(p-toluenesulfonyl)indole (3b)[12] was obtained in 96% yield. Similarly, The reaction of the indole 2 with 3-chloro-2-methylpropene, chloroacetonitrile, and benzyl bromide gave the corresponding 4-mercaptoindoles 3c (R=2-methyl-2-propen-1-yl), 3d (R=CH_2CN), and 3e (R=CH_2Ph), respectively. The results were summarized in Table I. Thus, considering the instability of 3a, we recommend to use the xanthate 2 as a stable equivalent of the mercaptan 3a. The S-



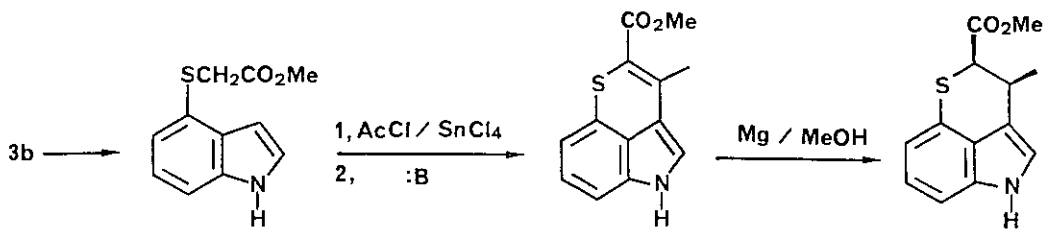
1 2 3

Table 1. Synthesis of 4-Mercaptoindoles (3).

Halide	4-Mercaptoindole			
		R	M p (°C)	Yield (%)
-----	3a	H	104 - 106	94
$ClCH_2CO_2Et$	3b	$-CH_2CO_2Et$	61.5 - 62.5	96
	3c		Oil	93
$ClCH_2CN$	3d	$-CH_2CN$	89.5 - 90.5	93
$PhCH_2Br$	3e	$-CH_2Ph$	119 - 122	81

substituted 4-mercaptoindoles 3b-e were, of course, able to be synthesized by the condensation of 3a with the halides under the basic conditions.

The sulfide 3b was easily hydrolyzed with KOH in methanol to afford methyl ester of 4-indolylthioacetic acid (95%) after workup with diazomethane. According to Kozikowski's method, the ester 4 was transformed into methyl ester of dehydrochuangxinmycin 5. The reduction of 5 to methyl ester of chuangxinmycin 6 has remained as a troublesome problem.[13] We found that a classical reduction system, Mg in methanol, was rather prefer to give 6 together with its trans-isomer (cis:trans = 2:1) in 70% yield.



4 5 6

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3. T. B. Kline, F. Benington, R.D. Morin, and J. M. Beaton, J. Med. Chem., 1982, 25, 908.

4. 4-Mercaptoindoles have been synthesized from 6-mercapto-2-nitrotoluenes by means of Reissert synthesis or of Leimgruber-Batcho reaction. E. P. Piers, V. B. Haarstad, R. J. Cushley, and R. K. Brown, Can. J. Chem., 1962, 40, 511. See also refs. 2 and 3.

5. Analogous xanthate was already reported to form from a 4-aminoindole through the corresponding diazonium salt: 4-(ethoxythiocarbonylthio)-1-(methoxycarbonyl)indole was synthesized in 59.5% together with 1-(methoxycarbonyl)indole (14.3%) by treatment of 4-amino-1-

methoxycarbonylindole with $NaNO_2$/HCl followed by the reaction with KSCSOEt.[6] This xanthate was hydrolyzed with NaOH/MeOH to yield 4-mercaptoindole (67.4%) and the corresponding disulfide (14%).[6]

6. M. Somei, J. Syn. Org. Chem., Japan, 1982, 40, 387. See also ref. cited therein.
7. M. Somei and M. Tsuchiya, Chem. Pharm. Bull., 1981, 29, 3145.
8. M. Matsumoto, Y. Ishida, and N. Hatanaka, Heterocycles, 1986, 24, 1667.
9. Pale yellow needles (from hexane-ethyl acetate) melted at 93-94 °C. NMR($CDCl_3$) δ1.12(t, J=7.0Hz, 3H), 2.33(s, 3H), 4.52(q, J=7.0Hz, 2H), 6.76(d, J=3.5Hz, 1H), 7.13-7.46(m,4H), 7.65(d, J=3.5Hz, 1H), 7.60-8.18(m,3H)ppm. IR(KBr) 1595, 1368, 1230, 1165cm^{-1}. Mass(m/z, %) 391(M^+, 17), 331(20), 303(31), 176(48), 155(35), 148(57), 91(100). Anal. Calcd. ($C_{18}H_{17}NS_3O_3$): C,55.22; H,4.38; N,3.58; S,24.57. Found: C,55.02; H,4.47; N,3.52; S,24.63.
10. K. Mori and Y. Nakamura, J.Org. Chem., 1969, 34, 4170.
11. NMR($CDCl_3$) δ2.30(s, 3H), 3.48(s, 1H), 6.70(d, J=3.8Hz, 1H), 7.10-7.30(m,4H), 7.61(d, J=3.8Hz, 1H), 7.68-7.94(m, 3H)ppm. IR(KBr) 2570, 1595, 1370, 1165 cm^{-1}. Mass(m/z, %) 303(M^+, 59), 155(19), 148(100), 91(54). Anal. Calcd. ($C_{15}H_{13}NS_2O_2$): C,59.38; H,4.32; N,4.62; S,21.13. Found: C,59.25; H,4.41; N,4.58; S,20.95.
12. NMR($CDCl_3$) δ1.10(t, J=7.1Hz, 3H), 2.33(s,3H), 3.62(s,2H), 4.08(q, J=7.1Hz, 2H), 6.86(d, J=3.8Hz, 1H), 7.14-7.42(m,4H), 7.62(d, J=3.8Hz, 1H), 7.14-7.42(m, 4H), 7.62(d, J=3.8Hz, 1H), 7.70-8.00(m, 3H)ppm. IR(KBr) 1725, 1596, 1367, 1167 cm^{-1}. Mass(m/z,%) 389(M^+, 100), 234(32), 162(43), 91(50). Anal. Calcd. ($C_{19}H_{19}NS_2O_4$): C,58.59; H,4.92; N,3.60; S,16.46. Found: C,58.62; H,5.01; N,3.55; S,16.34.
13. The hydrogenation of C-C double bond on the C-ring of 5 tended to accompany with rapid desurfurization.[2]

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