SYNTHESIS OF A NEW SKELETON, 2,6-EPITHIO-3-BENZAZOCINE

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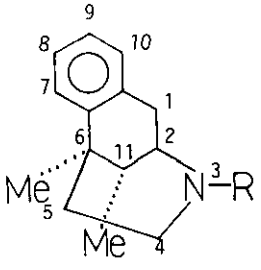
Abstract — Treatment of isothiochroman 2-oxide derivative (9) with acetic anhydride followed by heating in Dowtherm A (a mixture of biphenyl and diphenyl ether) afforded a novel 2,6-epithio-3-benzazocine derivative (2).

In connection with our study on sulfur-containing analgesic compounds, thieno[3,4-b]morphinans,[1] 8-mercapto-3-benzazocines,[2] and [1]benzothiopyrano[3,4-b]pyrroles[3] have been synthesized in our laboratory.

It is already known that 3-benzazocines (3) had not clinically shown analgesic activity.[4] 2,6-Epithio-3-benzazocines (2) were designed on the assumption that the epithiobenzazocines (2) would be metabolized with a radical cleavage of the C-S bond to give non-analgesic 3-benzazocine derivatives.[5] Therefore, the epithiobenzazocines (2) would be a candidate for the non-narcotic analgesics. In this communication, the synthesis of 3-ethoxycarbonyl-1,1,6-trimethyl-2,6-epithio-3-benzazocine is described in order to learn the chemical properties of the 2,6-epithio-3-benzazocine skeleton in which the carbon atom of 11-position of benzomorphans (1) is displaced by a sulfur atom.



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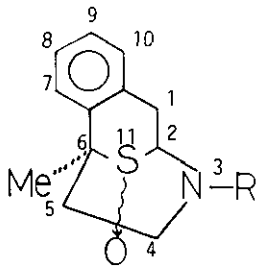

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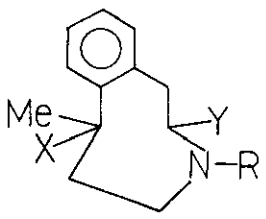

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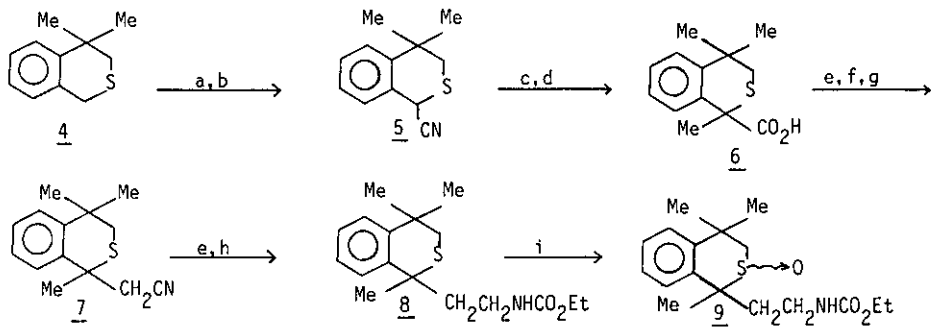
1-(2-Ethoxycarbonylaminoethyl)-1,4,4-trimethylisothiochroman 2-oxide (9), a key intermediate for the synthesis of 2,6-epithio-3-benzazocine skeleton, was synthesized from 4,4-dimethylisothiochroman (4) in several steps as shown in Chart 1.



a. SO_2Cl_2 b. $Hg(CN)_2$ c. NaH-MeI d. KOH e. $LiAlH_4$ f. CCl_4-PPh_3 g. KCN
h. $ClCO_2Et$, $NaHCO_3$ i. m-CPBA

Chart 1

4,4-Dimethylisothiochroman (4)[6] was chlorinated with sulfuryl chloride and treated with mercuric cyanide to give 1-cyano-4,4-dimethylisothiochroman (5). The cyanide (5) was methylated with sodium hydride and methyl iodide, and then the cyano group was hydrolyzed with KOH to lead to isothiochroman-1-carboxylic acid (6). The acid (6) was submitted to reduction with $LiAlH_4$ and the resulting alcohol was chlorinated with CCl_4-PPh_3. Treatment of the chloride with KCN gave the cyanide (7). Reduction of the cyanide (7) with $LiAlH_4$ and then treatment with ethyl chlorocarbonate gave 1-(2-ethoxycarbonylaminoethyl)isothiochroman (8).

In order to cyclize the compound (8) under the Pummerer reaction conditions,[7] the compound (8) was oxidized with m-CPBA to give the sulfoxide (9), which was a diastereoisomeric mixture in the ratio of 1:1.

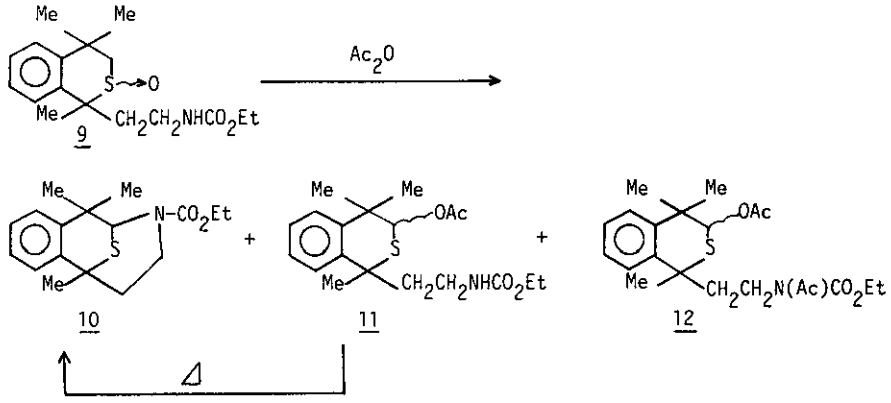
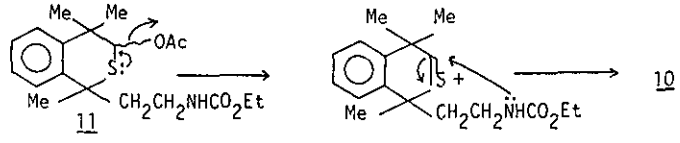


Chart 2

The sulfoxide (9) was refluxed in acetic anhydride for 24 hr to give the desired sulfide (10)[8] (18%), the 3-acetoxy product (11) (34.1%), and 3-acetoxy-N-acetyl compound (12) (45.0%). When the reaction was followed by TLC, it was observed that the compound (11) appeared first and then was converted into 10 and 12. On refluxing 9 in acetic anhydride for 1 hr 11 was obtained in 86.6% yield. Therefore, the cyclization conditions of 11 to 10 were investigated and we found the optimal conditions that the sulfide (11) was heated in Dowtherm A at 200 °C for 2.5 hr to give 10 in 71.3% yield. As a result, 2,6-epithio-3-benzazocine (10) has been eventually synthesized from 9 via 11 in 61.7% yield.

Since the sulfide (11) was a diastereomeric mixture in the ratio of 1:1 and the yield was over 50%, the cyclization reaction in Dowtherm A is considered to proceed definitely via the S_N2 mechanistic path in view of the recent work of Uchida and Oae.[9]



The structure of 10 was determined by the ^{1}H-nmr spectral data showing two singlets at 5.08 and 5.27 ppm, which were attributable to 2-H. This observation could be explained in terms of tautomerism of the urethane moiety.

Pharmacological evaluations of 2,6-epithio-3-benzazocine derivatives are now in progress.

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8. 10: Ir (KBr) cm^{-1}: 1700 (C=O). ^{1}H-Nmr ($CDCl_3$) δ: 1.27 and 1.32 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 1.44 and 1.50 (3H, s, 1-H), 1.70 (3H, s, 6-CH_3), 3.20 (3H, m, 4-H and 5-H), 3.90 - 4.50 (1H, m, 4-H), 4.21 and 4.24 (2H, q, J=7.0 Hz, $\underline{CH_2}CH_3$), 5.08 and 5.27 (1H, s, 2-H), 7.20 - 7.50 (4H, m, ArH). MS m/e: 305 (M^+), 158 (base).

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