FORMATION OF NOVEL HETEROCYCLES, [1]BENZOTHIOPYRANO[3,4-b]PYRROLE DERIVATIVES BY UNUSUAL CYCLIZATION REACTION OF 1-BENZOTHIOPYRAN-1-OXIDE DERIVATIVES

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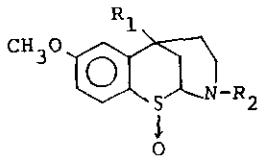
Abstract—Treatment of 1-benzothiopyran-1-oxide derivatives (12a,b) with sulfuryl chloride and then with sodium hydride afforded a novel type of derivatives of [1]benzothiopyrano[3,4-b]pyrrole.

Some sulfur-containing compounds, including thiambutene, thienomorphans, thiazolomorphans, S-metazocine, S-etorphine, etc., possess analgesic activity.[1] These compounds have sulfur atom in the aromatic moiety. No study has been reported on analgesic compounds possessing sulfur atom in the alicyclic moiety. In the course of our study on such sulfur-containing compounds, we found that unusual cyclization reaction of 1-benzothiopyran-1-oxide derivatives (12a,b) gave the novel heterocycles, [1]benzothiopyrano[3,4-b]pyrrole derivatives (2) in place of the usual products (1).



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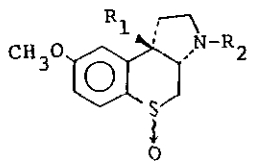
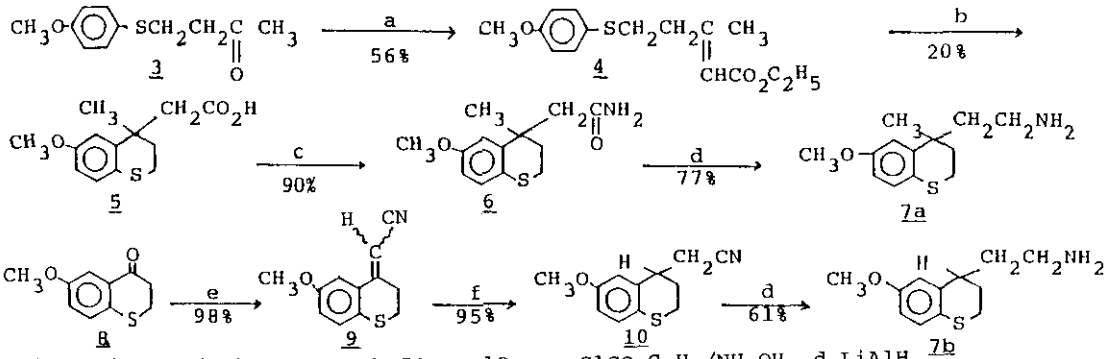


2

a; $R_1=CH_3$, $R_2=CO_2C_2H_5$
b; $R_1=H$, $R_2=CO_2C_2H_5$

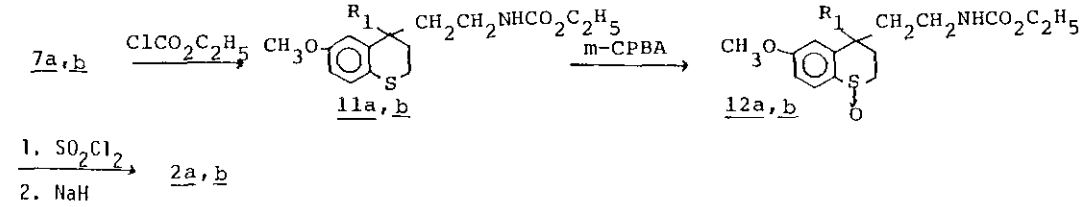
4-(2-Aminoethyl)-1-benzothiopyran derivatives (7a,b)[2] were synthesized by sequence of the reactions shown in Scheme 1 from 4-(4-methoxyphenylthio)-2-butanone (3)[3] and 6-methoxy-3,4-dihydro-2H-1-benzothiopyran-4-one (8),[4] respectively.



a. $(C_2H_5O)_2POCH(Na)CO_2C_2H_5$ b. 70%-$HClO_4$ c. $ClCO_2C_2H_5/NH_4OH$ d. $LiAlH_4$ e. $(C_2H_5O)_2POCH(Na)CN$ f. Mg

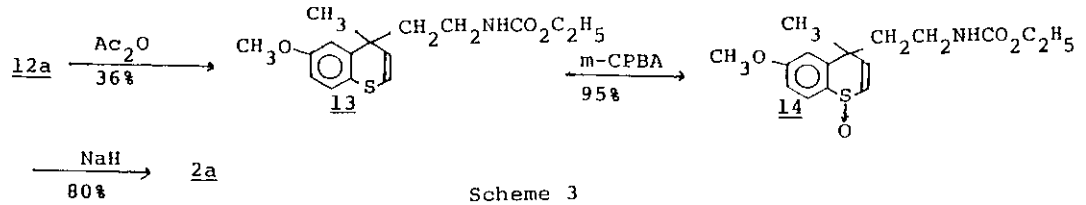
Scheme 1

A solution of the amines (7a,b) in benzene was refluxed with ethyl chlorocarbonate to give the carbamates (11a,b) in 84% and 94% yields. Then, 11a,b were oxidized with m-chloroperbenzoic acid (m-CPBA) in dichloromethane to give the sulfoxides (12a,b) in 90% and 92% yields. The 2-position of 11a,b could not be chlorinated with N-chlorosuccinimide (NCS) or sulfuryl chloride, so 11a,b were led to the corresponding sulfoxides (12a,b) to activate this position. The sulfoxides (12a,b) were chlorinated easily with sulfuryl chloride in dichloromethane,[5] and the resulting unstable chlorides were immediately treated with sodium hydride in refluxing THF to give the novel cyclized products (2a,b)[2] in 28% and 52% yields as diastereomeric mixtures (Scheme 2).



Scheme 2

The structure of 2a,b was speculated as [1]benzothiopyrano[3,4-b]pyrrole derivatives from the NMR data. Furthermore, it was identified by comparison with an authentic sample prepared by alternative synthetic route shown in Scheme 3.



Scheme 3

Pummerer reaction of 12a gave the vinyl sulfide (13)[2] and oxidation of 13 with m-CPBA gave the cyclic vinyl sulfoxide (14).[2] Generally, addition reaction of nucleophiles to vinyl sulfoxide proceeds through Michael-type reaction.[6] The reaction of 14 with sodium hydride gave the Michael-type adduct (2a). Thus, the cyclization of 12a,b was supposed to proceed by Michael-type addition of type 14 derived from dehydrochlorination of the unstable chlorides with sodium hydride, but not usual S_N2 reaction.[7] Finally, cis-fused ring system of 2a,b was confirmed by X-ray crystallography of one of the isomers of 2a.

Pharmacological results and stereochemistry of [1]benzothiopyrano[3,4-b]pyrrole derivatives will be published elsewhere.

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2. 7a ; IR(NaCl) cm^{-1}: 3320(NH_2). ^{1}H-NMR($CDCl_3$) δ: 1.38(2H, s, NH_2), 1.41(3H, s, C_4-CH_3), 1.55-2.40(4H, m, C_3-H_2 and C_4-$\underline{CH_2}CH_2N$), 2.50-3.15(4H, m, C_2-H_2 and C_4-$CH_2\underline{CH_2}N$), 3.76(3H, s, OCH_3), 6.66(1H, dd, J=9.0 and 3.0 Hz, C_7-H), 6.88(1H, d, J=3.0 Hz, C_5-H), 7.02(1H, d, J=9.0 Hz, C_8-H). MS m/e : 237(M^+, base).

7b ; IR(NaCl) cm^{-1}: 3330(NH_2). ^{1}H-NMR($CDCl_3$) δ: 1.50-2.30(4H, m, C_3-H_2 and C_4-$\underline{CH_2}CH_2N$), 2.31(2H, br, NH_2), 2.60-3.35(5H, m, C_2-H_2, C_4-H and C_4-$CH_2\underline{CH_2}N$), 3.76(3H, s, OCH_3), 6.55-6.85(2H, m, C_5-H and C_7-H), 7.05(1H, d, J=9.0 Hz, C_8-H). MS m/e : 223(M^+, base).

2a ; diastereomeric mixture in the ratio 2:1 : IR(NaCl) cm^{-1}: 1695(C=O), 1030(SO). ^{1}H-NMR($CDCl_3$) δ : 1.31 and 1.32(3H, t, J=7.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.40 and 1.55(3H, s, C_{9b}-CH_3), 1.85-2.75(3H, m, C_1-H_2 and C_{3a}-H), 3.40-4.85(4H, m, C_2-H_2 and C_4-H_2), 3.85 (3H, s, OCH_3), 4.21 and 4.23(2H, q, J=7.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.75-7.10(2H, m, C_7-H and C_9-H), 7.50-7.75(1H, m, C_6-H). MS m/e : 323(M^+), 191(base).

2b ; diastereomeric mixture in the ratio 3:1 : IR(NaCl) cm^{-1}: 1685(C=O), 1035(SO). ^{1}H-NMR($CDCl_3$) δ : 1.30(3H, t, J=7.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.60-4.75(8H, m, C_1-H_2, C_2-H_2, C_{3a}-H, C_4-H_2 and C_{9b}-H), 4.24 and 4.26(2H, q, J=7.0 Hz, $CO_2\underline{CH_2}CH_3$), 3.86(3H, s, OCH_3), 6.70-7.40(2H, m, C_7-H and C_9-H), 7.25 and 7.80(1H, d, J=9.0 Hz, C_6-H). MS m/e : 309(M^+), 177(base).

13 ; IR(NaCl) cm^{-1}: 3340(NH), 1710(C=O), ^{1}H-NMR($CDCl_3$) δ : 1.20(3H, t, J=7.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.44(3H, s, C_4-CH_3), 1.50-2.25(2H, m, C_4-$\underline{CH_2}CH_2N$), 2.85-3.50(2H, m, C_4-$CH_2\underline{CH_2}N$), 3.78(3H, s, OCH_3), 4.06(2H, q, J=7.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.50-5.00(1H, br, NH), 5.57(1H, d, J=9.75 Hz, C_3-H), 6.08(1H, d, J=9.75 Hz, C_2-H), 6.74(1H, dd, J= 9.0 and 3.0 Hz, C_7-H), 6.93(1H, d, J=3.0 Hz, C_5-H), 7.10(1H, d, J=9.0 Hz, C_8-H). MS m/e : 307(M^+), 191(base).

14 ; diastereomeric mixture in the ratio 2.5:1 : IR(NaCl) cm^{-1}: 3300(NH), 1710(C=O), 1030(SO). ^{1}H-NMR($CDCl_3$) δ : 1.14 and 1.18(3H, t, J=7.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.37 and 1.60(3H, s, C_4-CH_3), 1.50-3.25(4H, m, C_4-CH_2CH_2N), 3.87(3H, s, OCH_3), 4.05 and 4.14(2H, q, J=7.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.95-5.40 and 5.60-6.10(1H, br, NH), 6.34 and 6.44(1H, d, J=10.5 Hz, C_3-H), 6.50-7.30(3H, m, C_2-H, C_5-H and C_7-H), 7.65-8.00(1H, m, C_8-H). MS m/e : 323(M^+), 191(base).

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