THE SYNTHESIS OF THIENOTRIAZOLOTHIAZEPINES

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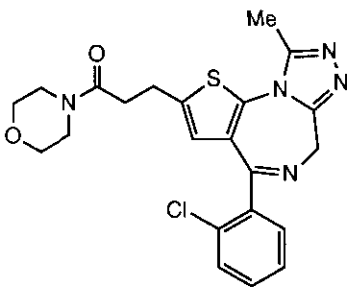
Abstract——Some derivatives of thienotriazolothiazepine, a novel heteroazepine, were synthesized. These compounds showed anti-PAF activity.

In 1986, WEB-2086 (**1**), which is characterized by its thienotriazolodiazepine skeltone, was reported to exhibit anti-PAF (platelet activating factor) activity.[1] Following this report, a number of thienotriazolodiazepine derivatives have been synthesized and tested for their anti-PAF activity.

In a search for potent and orally active PAF antagonists, we were interested in this structure and planed to synthesize its structurally related analogue, thienotriazolothiazepines (**2**). While some benzotriazolothiazepines (**3**) have been reported,[2] there have, to the best of our knowlege, been no report on the synthesis of thienotriazolothiazepines. Now, we report the first synthesis of thienotriazolothiazepines.

Synthetic route is shown in Scheme I. First, the α-cyanoketone (**4**)[3] was treated with 1,4-dithiane-2,5-diol and Et_3N[4] or 1-butanal, sulfur and Et_3N[5] to give the 2-aminothiophene (**5a**, 49%) or its ethyl analogue (**5b**, 57%), respectively. Protection of the amino group of **5** with t-butoxycarbonyl (Boc) group (**6a**: 63%, **6b**: 64%) followed by reduction ($NaBH_4$, DMF) furnished the alcohols (**7a**: 88%, **7b**: 76%).



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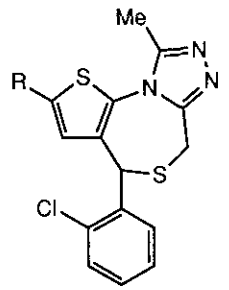
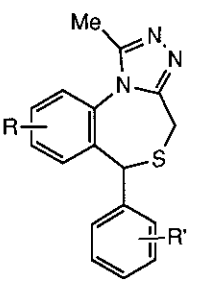


2 a: R=H
b: R=Et
c: R=Br



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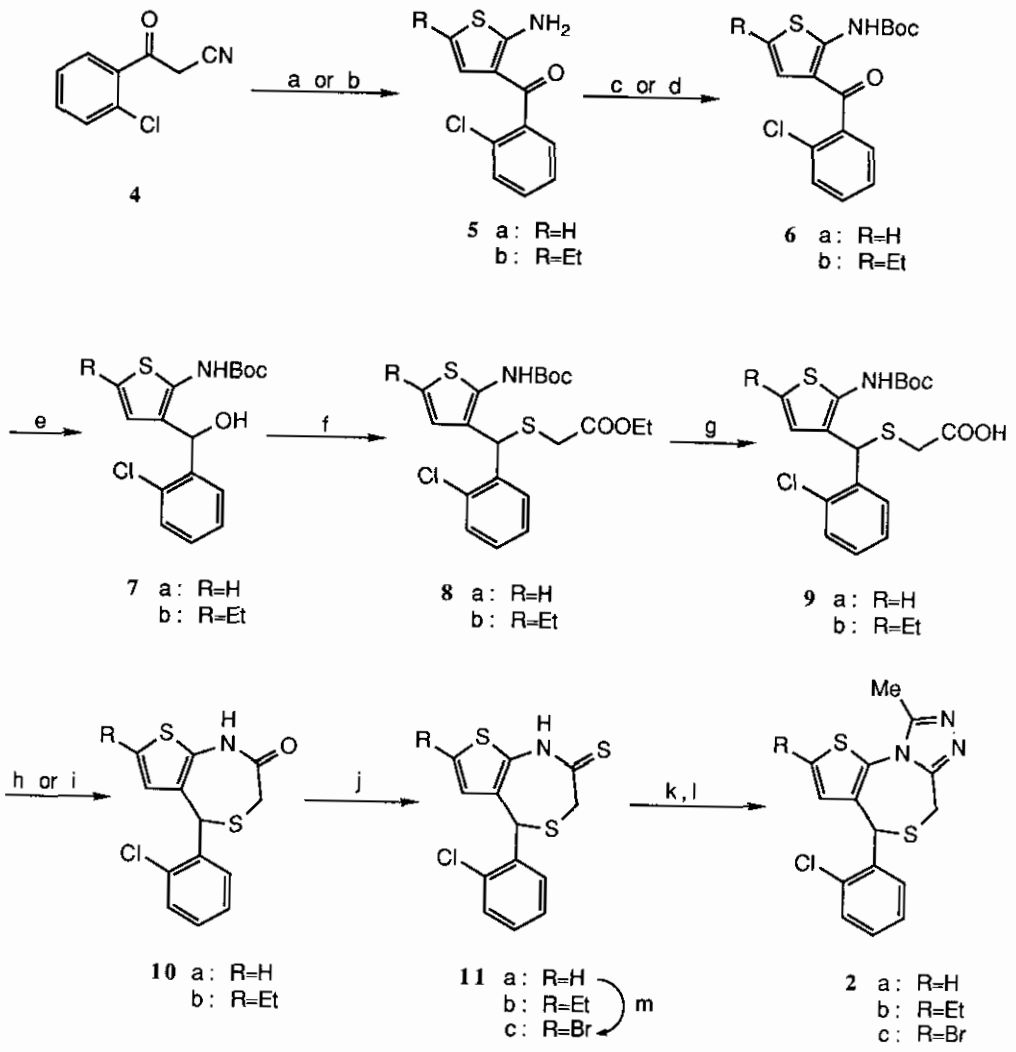
Scheme I



a) 1,4-dithiane-2,5-diol, Et_3N, dioxane, b) 1-butanal, sulfur, Et_3N,
c) Boc_2O, 10%NaOH *aq*., THF, d) NaH, Boc_2O, DMF, e) $NaBH_4$, DMF,
f) PPh_3, DEAD, ethyl thioglycolate, benzene, g) 10%NaOH *aq*., MeOH,
h) $(COCl)_2$, DMF, CH_2Cl_2, i) $(COCl)_2$, DMF, CH_2Cl_2 then TFA,
j) Lawesson's reagent, toluene, k) $H_2NNH_2 \cdot H_2O$, THF, l) $MeC(OMe)_3$,
m) Br_2, pyridine

The alcohols (**7**) were treated under Mitsunobu conditions (Ph_3P, DEAD, ethyl thioglycolate, benzene) to provide the sulfides[6] (**8a** :35%, **8b**: 68%), which were hydrolyzed to give the carboxylic acids (**9a**: 97%, **9b**: 92%).

Now that we obtained the desired precursor for the thiazepine ring, the stage was set for the cyclization. Cyclization of **9** to the thiazepine (**10**) was effected by treatment with oxalyl chloride (**10a**: 14%) or with oxalyl chloride and trifluoroacetic acid (**10b**: 67%).

The construction of the triazole ring was readily performed under the conventional conditions. Treatment of **10** with Lawesson's reagent[7] gave the thioamide (**11a**: 97%, **11b**: 77%). At last, **11** was converted into the thienotriazolothiazepine (**2a**: 37%, **2b**: 47%)[8] by the succesive treatment with hydrazine monohydrate and trimethyl orthoacetate. In the same manner, the bromide (**2c**)[8] was obtained in 57% yield from **11c** ,which was prepared from **11a** by bromination(Br_2, pyridine; 95%).

Thienotriazolothiazepines (**2**) were tested for their activity in inhibiting rabbit platelet aggregation induced by PAF.[9] All compounds synthesized here exhibited anti-PAF activity (Table1).

Thus we achieved a synthesis of a novel heteroazepine, thienotriazolothiazepines, which showed anti-PAF activity.

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Table 1. Inhibition of PAF(10^{-8}M)-induced Platelet Aggregation in Rabbit P.R.P.

Compound	$IC_{50}(10^{-6}M)$
2a	21
2b	(42%)*
2c	26

* Inhibition of platelet aggregation at the cocentration of 10^{-4}M

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6) Bromination (Br_2, Ph_3P or NBS, Ph_3P) or mesylation (MsCl, Et_3N) of 4a failed,presumably because of the lability of the product.

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8) **2a**, ^{1}H Nmr (100 MHz, $CDCl_3$, TMS)δ : 2.43 (3H, s), 3.83 (1H, d, J=14Hz), 3.95 (1H, d, J=14Hz), 5.73 (1H, s), 6.35 (1H, d, J=6Hz), 6.76 (1H, d, J=6Hz), 7.17-7.42 (3H, m), 7.55-7.67 (1H, m); ms m/z: 333 (M^+).

2b; ^{1}H Nmr (100MHz, $CDCl_3$, TMS)δ : 1.30 (3H, t, J=8Hz), 2.39 (3H, s), 2.80 (2H, q, J=8Hz), 3.94 (1H, d, J=14Hz), 3.98 (1H, d, J=14Hz), 5.64 (1H, s), 6.39 (1H, s), 7.19-7.40 (3H, m), 7.48-7.61 (1H, s); ms m/z: 361 (M^+).

2c; ^{1}H Nmr (100MHz, $CDCl_3$, TMS)δ : 2.39 (3H, s), 3.90 (1H, d, J=20Hz), 3.93 (1H, d, J=20Hz), 5.69 (1H, s), 6.74 (1H, s), 7.19-7.36 (3H, m), 7.48-7.64 (1H, m); ms m/z: 413(M^+).

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