A Simple Synthesis of 1-Phenothiazineethanolamines: Potential Antimalarials

Ângelo C. Pinto* and Rosaly S. da Silva

Núcleo de Pesquisas de Produtos Naturais, Instituto de Ciências Biomédicas Bloco H, Universidade Federal do Rio de Janeiro-Ilha do Fundão Rio de Janeiro ZC-32, Brasil

Richard A. Hollins

Instituto Militar de Engenharia Praia Vermelha, Rio de Janeiro ZC-82, RJ, Brasil

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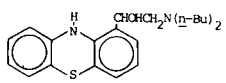
Two routes for the synthesis of the 1-phenothiazineethanolamine (**4**) starting from 1,2-dioxo-1,2-dihydropyrrolo[3,2,1-*kl*]phenothiazine are described.

J. Heterocyclic Chem., 16, 1085 (1979).

Sir:

A variety of aromatic ethanolamines have been reported to be antiparasitic or antimalarial agents (1-6). Nodiff, *et al.*, reported the synthesis of α-(di-*n*-butylaminomethyl)-1-phenothiazinemethanol (**1**), which was shown to have two times the antimalarial activity of quinine and to be non-toxic in the range tested (6). The synthetic scheme followed, however, resulted in a low yield and poses certain difficulties to preparation on a larger scale. Since the only such derivative prepared (**1**) possessed such activity, we felt it was warranted to investigate other routes of synthesis for making these promising derivatives more readily available for screening.

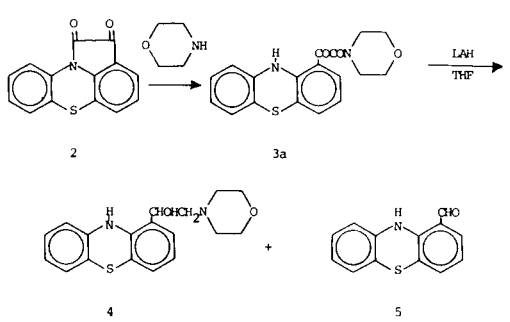
Structure 1



1

We recently reported (7) the facile and high yield ring opening reaction of 1,2-dioxo-1,2-dihydropyrrolo[3,2,1-*kl*]-phenothiazine (**2**) with amines. The resulting keto-amides (**3**) appeared to be good candidates for transformation into the desired ethanolamine system and, indeed, lithium aluminum hydride reduction of the morpholine derivative **3a** furnished amino-alcohol **4**, m.p. 140-141°, in 50% yield accompanied by the formation of phenothiazine-1-carboxaldehyde (**5**) in about 12% yield (Scheme I) (8).

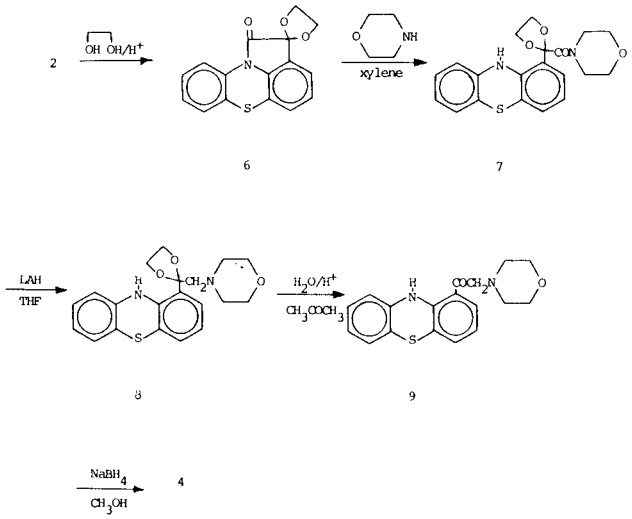
Scheme I



2 3a 4 5

We also investigated a lengthier route wich allowed independent reductions of the carbonyl functions. The treatment of **2** with ethylene glycol readily furnished ketal **6** (91% yield), m.p. 197°, which underwent ring opening upon treatment with morpholine, producing ketal-amide **7**, m.p. 120-121° (72% yield; 97% based upon recovered **6**). Then, without isolating intermediates, **7** was reduced with lithium aluminum hydride, the ketal group removed and finally reduction with sodium borohydride furnished **4** in 69% yield (from **7**) (Scheme II).

Scheme II



6 7 8 9 4

Although this latter route requires more steps, not all intermediates need to be isolated, the yield is higher considering recovered **6** and it should also be possible to perform an asymmetric reduction in the last step. In general, however, both routes are convenient and should provide ready access to a large number of these derivatives.

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(8) All new isolated componds presented satisfactory elemental analyses or high resolution mass spectra.