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SOME TRICYCLIC ANNELATED QUINAZOLINES

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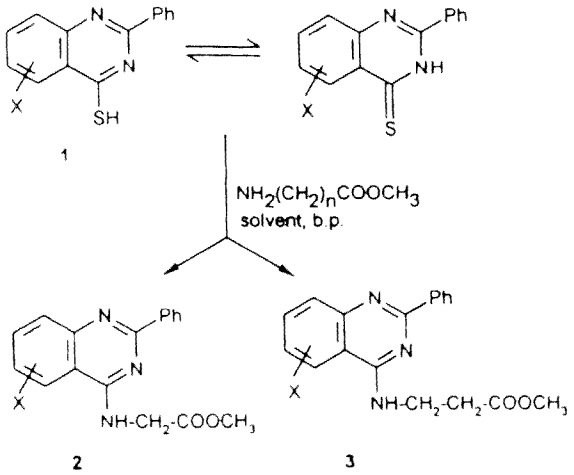
Preparation of some imidazo[1,2-c]- and pyrimido[1,2-c]quinazolines by the reaction of the corresponding 3H-quinazoline-4-thiones with amino acid esters is described.

The quinazoline ring system has been found to be a constituent of many bioactive natural compounds. Commercially available derivatives of this type, among other pharmaceuticals and pesticides, arouse interest in synthesis and testing of quinazolines. Great interest has been focused on condensed quinazolines, as a synergic effect owing to combination with other pharmacophores or even an entirely novel type of activity can be expected in these compounds [1, 2].

Tricyclic annelated derivatives of quinazoline exhibit interesting biological activity. Most of them, such as imidazo[1,2-c]- and pyrimido[1,2-c]quinazolines show marked adrenomimetic, broncholytic, psychoanaleptic, and anti-depressant properties [3-5]. The most common way for preparation of the mentioned annelated quinazolines involves reactions of 4-chloro- or 2,4-dichloroquinazolines with aziridine, ethylenediamine, or amino alcohol followed by cyclization in the presence of a suitable condensation agent [5-7].

In the present work, we describe preparation of similar annelated quinazoline derivatives directly from the substituted 2-phenyl-3H-quinazoline-4-thiones (**1**), which are easily synthesized from the available N-phenylbenzimidoyl chloride, according to the procedures described in [8]. Unlike their oxy analogues, easy enolization of the thioamide group in the thione **1** enables direct substitution of the thiol group with an amino group of the corresponding amino acid. For this purpose we prepared four different substituted quinazoline-4-thiones (X = H, 6-Cl, 6-Br, 6-CH_3).



The reactions of thiones **1** with selected amino acid esters in boiling solvent, under the basic catalysis, afforded the corresponding substitution products **2**, **3** in low yield. Variation of reaction conditions led us to the conclusion that esters of amino acids reacted very reluctantly and that this approach is of little preparative value.

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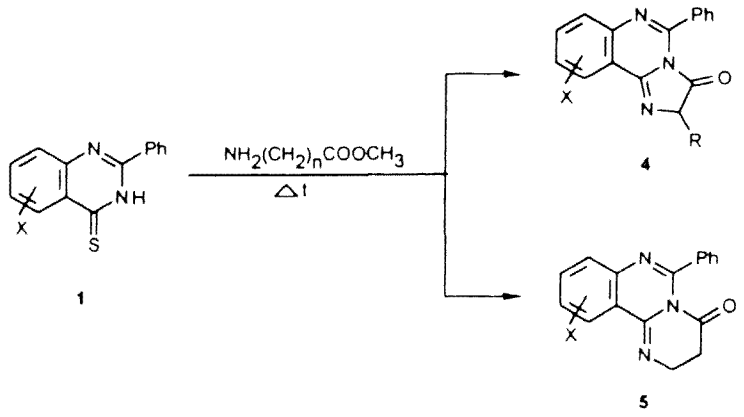
The procedure could be improved significantly by carrying it out without a solvent. At the melting temperature, when the reaction mixture becomes homogeneous not only nucleophilic substitution was facilitated but a thermal cyclization elicited, thus directly affording 3-oxo-2H-imidazo[1,2-c]quinazolines (**4**) and 4-oxo-2,3-dihydropyrimido[1,2-c]quinazolines (5).



The structure of all prepared compounds were in accord with their analytical, IR, and ^1H NMR spectral data.

Spectral data of prepared compounds **2** and **3**:

IR (cm^{-1}): 1720-1743 $\nu C{=}O$,1603-1610 $\nu C{=}N$, 1200-1217 $\nu C-O$;

^1H NMR (δ, ppm): **2** ~3.5 (s, 3H, OCH_3), ~4.2 (s, 2H, CH_2), ~13.9 (bs, 1H, NH); **3** ~2.18 (t, 2H, CH_2N), ~2.88 (t, 2H, CH_2CO), ~3.58 (s, 3H, OCH_3), ~14.14 (bs, 1H, NH).

Spectral data of prepared compounds **4** and **5**:

4: IR (cm^{-1}): 1664-1668 $\nu C{=}O$, 1602-1608 $\nu C{=}N$ ^1H NMR (δ, ppm): R = H ~5.80 (s, 2H, CH_2); R = CH_3 ~1.23 (d, 3H, CH_3), ~3.83 (q, 1H, CH);

5: IR (cm^{-1}): 1660-1664 $\nu C{=}O$, 1603-1608 $\nu C{=}N$ ^1H NMR (δ, ppm): ~2.66 (t, 2H, CH_2N), ~3.60 (t, 2H, CH_2CO).

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