SYNTHESIS OF 2-SUBSTITUTED NAPHTH[1,8-de]-1,3-OXAZINES

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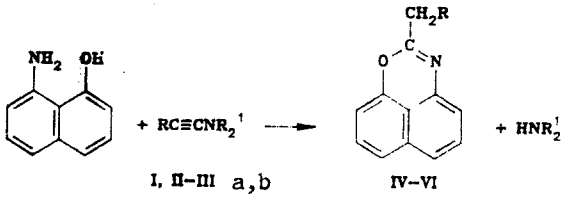
2-Substituted naphth[1,8-de]-1,3-oxazines with an unsaturated but nonconjugated fragment have been synthesized by treating alkenylynamines with 1,8-aminonaphthol.

Methods for preparing naphth[1,8-de]-1,3-oxazines have recently been devised, e.g., a multistage synthesis based on pyridine has been described in [1]. The most successful method was proposed by Czech workers [2] and is based on the dyes brilliant red 3B or H acids. In this case the synthesized naphth[1,8-de]-1,3-oxazines contained sulfo groups at positions 3, 5, or 6, which could not be removed.

We have studied a method for preparing the title substances by reaction of simple ynamines and vinylacetylenyl ynamines of type I-III with 1,8-aminonaphthol analogous to the synthesis of naphth[1,2-de]oxazoles [3] and benzoxazole derivatives of the isoxazole [4].



I, II–III a,b IV–VI

I, IV R=CH_3, II, V R=CH_3CH=CH; III, VI R=$(CH_3)_2C$=CH; IIa, IIIa $R^1=C_2H_5$; IIb, IIIb $R^1=C_3H_7$

Compounds IV-VI were isolated by column chromatography.

The IR spectrum of IV showed absorptions for a carbon—nitrogen double bond at 1658 cm^{-1} and a carbon—oxygen bond at 1050 cm^{-1}. The PMR spectrum of IV showed ethyl group proton signals at 1.17 (3H, t, CH_3) and 2.33 ppm (2H, q, CH_2) and naphthyl ring protons as a multiplet at 6.3-7.5 ppm (6H).

The IR spectrum of V showed absorption for a nonconjugated carbon—carbon double bond in the side chain at 1615 cm^{-1} in addition to the absorption bands given above. In the PMR spectrum of VI signals were seen for two side chain methyl groups at 1.61 and 1.73 ppm (singlets, each 3H, CH_3), a methylene proton doublet at 2.98 ppm, and the vinyl proton as a triplet at 5.3 ppm (1H). The naphthalene ring protons were observed as a multiplet at 6.3-7.4 ppm (6H).

Thus, addition of the 1,8-aminonaphthol occurs regioselectively at the carbon—carbon triple bond. Compounds of a noncyclic structure were not found, in agreement with attack of both functional groups at the acetylenic $C_{(1)}$ atom.

EXPERIMENTAL

IR spectra were recorded on an IKS-29 spectrophotometer for a 100-micron film and PMR spectra on a Tesla BS-497 C (100 MHz) using HMDS internal standard. Column chromatography was carried out using L 100/250 silica gel (Czechoslovakia). Thin layer chromatography was performed on Silufol UV-254 plates using hexane—ether—10% aqueous ammonia (10:5:0.03) with iodine vapor visualization.

Elemental analytical data for C, H, and N for IV-VI agreed with those calculated.

2-Ethylnaphth[1,8-de]-1,3-oxazine (IV). The hydrochloride salt of 1,8-aminonaphthol (2.4 g) was suspended in absolute alcohol in an argon-filled flask, heated to reflux, sodium bicarbonate (1.2 g) was added, and 1-diethylamino-1-propyne (1.2 g) was added dropwise, not allowing the temperature to rise above 35°C. The mixture was stirred for 40 min until a sample showed the disappearance of the starting IR absorption for the acetylenic bond at 2200 cm^{-1} (C≡C). The precipitate was filtered off, washed with absolute alcohol, the solvent removed, and the precipitate distilled in vacuo to give 1.4 g of product (70%) with bp 102-103°C (1 mm) and mp 64°C (from hexane).

2-(2-Butenyl)naphth[1,8-de]-1,3-oxazine (V) was obtained similarly using 1-diethylamino-3-penten-1-yne (IIIa) or 1-dipropylamino-3-penten-1-yne (IIa) to give 1.5 g (69%) with mp 61°C (from hexane).

2-(3-Methyl-2-butenyl)naphth[1,8-de]-1,3-oxazine (VI) was prepared similarly from 1-diethylamino-3-methyl-3-penten-1-yne (IIb) or 1-dipropylamino-3-methyl-3-penten-1-yne (IIIb) to give 1.7 g (71%) with mp 69°C (from hexane).

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SYNTHESIS OF 6-PHENYLTHIOBENZO[b]THIOPHENES

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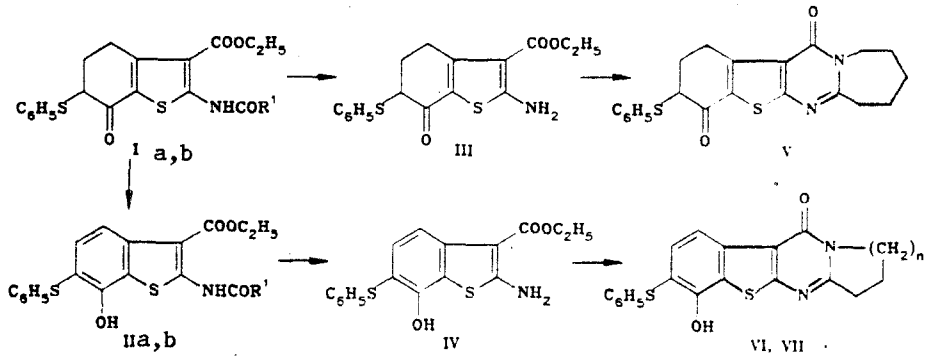
A method of synthesizing 2-acetylamino-7-hydroxy-6-phenylthio-3-carbethoxybenzo[b]thiophenes from 6-phenylthio-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes has been developed. A method is also proposed for synthesis of 7-phenylthiobenzothieno[2,3-d]pyrimidines.

In a number of examples the introduction of an alkylthio or arylthio group into bioactive substances can lead to an important change in their biological activity [1-4].

In continuation of our development of methods for synthesis of polyfunctional thiophenes and benzothiophenes having biological (in particular antiviral) activity [5], we have prepared 6-phenylthiobenzothiophenes. In [6] there was reported a synthesis of 6-bromo-7-hydroxybenzo[b]thiophenes by dehydrobromination of 6,6-dibromo-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes and the possibility of using the method for making substituted 6-phenylthiobenzo[b]thiophenes was also examined. Isolation of the intermediate 6-bromo-6-phenylthio-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes was not achieved due to spontaneous dehydrobromination to the 7-hydroxy-6-phenylthiobenzothiophenes IIa, b. The structures of the prepared compounds were proved by PMR and IR spectroscopy. For IIa the signals of the two 4-H and 5-H aromatic protons appeared at 7.42 and 7.80 ppm as doublets and the IR spectrum showed a phenolic hydroxyl group absorption band at 3400 cm^{-1}.



I, IIa $R^1=CH_3$, b $R^1=C_2H_5$; VI $n=1$, VII $n=3$

Thienopyrimidines as thiophene isosteres of quinazolines have been widely used as key compounds for synthesizing polyfunctional compounds with a broad spectrum of biological activity [8, 9]. In this connection, some previously unknown benzothienopyrimidines have been synthesized.

The acetyl groups of Ia and IIa were hydrolyzed using aqueous alcoholic base to prepare bifunctional 2-amino-3-carbethoxybenzo[b]thiophenes III and IV, which can be used for construction of the pyrimidine ring. The IR spectra of III and IV showed absorptions for the NH_2 group at 3240-3390 cm^{-1}.

Using a known method [9], the reaction of III and IV with lactams (pyrrolidone and caprolactam) in the presence of phosphorus oxychloride gave the 4,8-dioxo-7-phenylthio-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine V and the 8-hydroxy-4-oxo-7-phenylthiobenzothieno[2,3-d]pyrimidines VI and VII (Table 1).

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