REACTION MECHANISM FOR FORMATION OF CONDENSED THIENOPYRANS AND THIENOTHIOPYRANS

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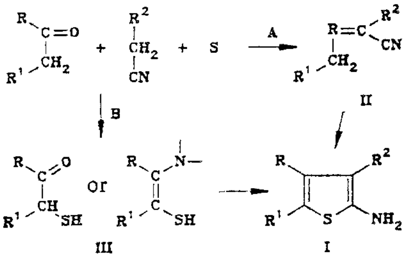
The formation of 2-amino-3-cyanothiophenes has been studied. It has been shown that the intermediates in the synthesis are the Knoevenagel type α,β-unsaturated nitriles.

2-Aminothiophenes (I) have been prepared by the base catalyzed Gewald reaction of carbonyl compounds with nitriles and powdered sulfur [1-3].

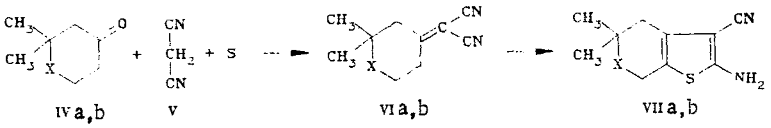


This is analogous to the Asinger reaction [4] in which α-mercaptocarbonyls or β-mercaptoenamines can be formed as intermediate compounds [5].

It was proposed [4] that the first stage of the reaction can involve the intermediate α,β-unsaturated nitriles II which subsequently cyclize in the presence of sulfur to 2-amino-3-substituted thiophenes I.

However it was not possible to make an unambiguous decision concerning the structure of the intermediate compounds on the basis of those studies. Whether they were the unsaturated nitriles II or the α-mercaptocarbonyl compounds III remained uncertain.

We have set ourselves the task of understanding the mechanism of the reaction and the structure of the intermediate formed in the synthesis of 2-aminothiophenes condensed to six-membered, saturated heterocycles containing oxygen and sulfur.



IV, VI, VIIa X=O, b X=S

Our investigations, in fact, have shown that the intermediates in the formation of the 2-amino-3-substituted thiophenes are the unsaturated nitriles VIa, b, which are the products of a Knoevenagel reaction. They take part in a cyclization reaction with sulfur to form the 2-amino-3-substituted thiophenes VIIa, b.

The course of the reaction was monitored by GLC, TLC, and by chemical means. A chromatogram of the reaction mixture (IVa, b, V, powdered sulfur in alcohol, and catalytic amounts of sulfur) was taken every minute for a total of 30 samples and interpreted knowing the chromatography of the individual components. The temperature was maintained at 13-15°C. The chromatograms show (Fig. 1) that the concentrations of pyranone IVa, thiopyranone IVb,

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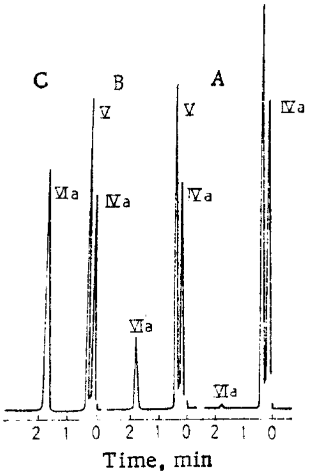

Fig. 1. Chromatogram of mixtures of IVa, V, and VIa on column 2: A) starting mixture of IVa and V; B) mixture after 1 min; C) mixture with added VIa.

and dinitrile V decrease with time while the peak for the compound formed (VI), which appears in the first minute, reaches a maximum after three minutes.

A parallel study was carried out by TLC to confirm these results. A low intensity spot appears within the first minute of the reaction corresponding to the dinitriles of 2,2-dimethyl-4-tetrahydropyranylidene and thiopyranylidenemalonic acids VIa, b. The intensity of the spot increases with time and reaches a maximum after three minutes. The reaction was also carried out in the absence of malondinitrile under the same conditions at 45°C. No substances other than starting materials were seen on the chromatographic plates, thus sulfur did not react with the investigated ketones IVa, b.

The proposed Gewald [4] mechanism (route A) was also confirmed chemically. Thus the crystalline reaction products separated ten minutes after the beginning of the reaction of IVa, b with V, powdered sulfur, and diethylamine in water at 13-15°C were identified as VIa, b from IR and PMR spectral data. At increased temperature the mixture of VIa, b reacts with sulfur and after 25 minutes completely precipitates the final products VIIa, b. The structures of the compounds obtained were confirmed by IR and NMR spectra in line with literature data [6].

Thus it is unambiguously shown that 2-aminothiophenes VIIa, b, formed by condensation with O- and S- containing six-membered heterocycles, takes place via intermediate α,β-unsaturated nitriles VIa, b (route A).

EXPERIMENTAL

TLC was carried out on Silufol UV-254 plates using chloroform—ethyl acetate—heptane (2:3:1, System A) or benzene—ether—heptane (2:2:1, System B) and visualized by UV light or iodine vapor. GLC was performed on a Chrom-5 PID instrument. The columns were glass (2 m × 3 mm) and were filled with 1) 7% OV-17 on Chromaton N-AW HMDS (0.125-0.160 mm) or 2) 5% XE-60 on Chromaton N-AW HMDS (0.160-0.200 mm). The carrier was nitrogen (40 ml/min). IR spectra were carried out on a UR-20 spectrometer in paraffin mull and PMR spectra on a Varian T-60 instrument using TMS as internal standard and CCl_4 solvent.

2,2-Dimethyl-4-tetrahydropyranylidenemalonitrile (VIa) [6]. A mixture of pyranone IVa (3.2 g, 25 mmole), malondinitrile (1.6 g, 25 mmole) and powdered sulfur (0.8 g, 25 mmole) in water (25 ml) was stirred at 20°C until complete solution of the dinitrile, and diethylamine (0.22 g, 30 mmole) was added over 1 min with the temperature maintained at 13-15°C. The mixture was then stirred for 1.5 h and the precipitate filtered and washed with cold water (3 × 10 ml). The mixture was treated with methanol (20 ml), the sulfur filtered off, and the solvent removed to give a residue which was recrystallized from hexane. The yield was 3.4 g (80%) with mp 36-38°C and R_f 0.70 (System A) in agreement with [6]. IR spectrum: 1590 (C=C), 2250 cm^{-1} (C≡N). PMR spectrum: 1.14 (6H, s, CH_3), 2.47 (2H, s, $C{=}C{-}CH_2$), 2.55 (2H, J = 5.7 Hz, $C{=}C{-}CH_2$), 3.67 ppm (2H, J = 5.7 Hz, CH_2O).

2,2-Dimethyl-4-tetrahydrothiopyranylidenemalondinitrile (VIb). A similar preparation as described above from thiopyranone IVb (3.6 g, 25 mmole), malondinitrile (1.6 g, 25 mmole), powdered sulfur (0.8 g, 25 mmole) and diethylamine (0.22 g, 30 mmole) in water (25 ml) gave VIb (3.2 g, 66.6%) with mp 36°C (hexane) and R_f 0.77 (B). From [6], mp = 34-35°C. IR spectrum: 1590 ($C{=}C$), 2250 cm^{-1} ($C{\equiv}N$). PMR spectrum: 1.37 (6H, s, CH_3), 2.80 (2H, s, $CH_2{-}C{=}C$), 2.90 ppm (4H, CH_2CH_2).

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TRANSFORMATIONS OF THE SULFUR ANALOGS OF β-CARBOLINS UNDER THE INFLUENCE OF NUCLEOPHILES*

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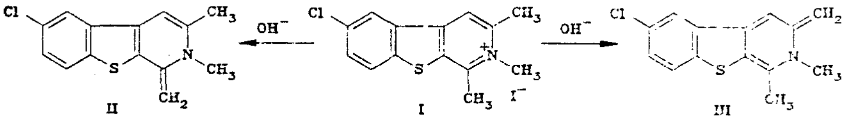
The reaction of the quaternary salts of some thienopyridines (the sulfur analogs of β-carbolins) with nucleophilic reagents was investigated. It was shown that either the methylene anhydro bases are formed or one or both heterocyclic rings are transformed, depending on the structure of the thienopyridine and on the reaction conditions.

Earlier [2] we showed that under the action of alcohol solutions of alkalis the quaternary salts of β-carbolins undergo a series of transformations both associated with the transformation of the ring and without such transformation. For instance, the reaction of the quaternary salts of β-carbolins not substituted at the NH group with alkali results in deprotonation with the formation of a stable anhydro base, which does not undergo further transformations. If, however, the NH group is substituted by an N-alkyl radical, the action of alkali leads to the products from the transformation of both rings (both the pyridine and the indole rings).

In the present work we undertook an investigation into the behavior of the quaternary salts of some thienopyridines (the sulfur analogs of β-carbolins) in reaction with nucleophiles. In the case of these compounds it is possible to trace the effect of the condensed thiophene ring on the reactivity of the adjacent pyridine ring and, in particular, in relation to nucleophilic reagents.

One of the subjects we selected for investigation was the methyl derivative of benzothioenopyridine (I), i.e., the closest structural analog of β-carbolins. It was found that the methiodide (I) eliminates a proton from one of the methylene groups in reaction with a methanol solution of methylamine and gives the stable methylene anhydro base (II). The formation of stable anhydro bases with an unsubstituted methylene group is an extremely rare effect, which is restricted to only a few examples [3, 4]:



II I III

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*For the previous communication, see [1].

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