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NUCLEOPHILIC ADDITION REACTIONS OF 3-KETOTHIOPHANE DERIVATIVES

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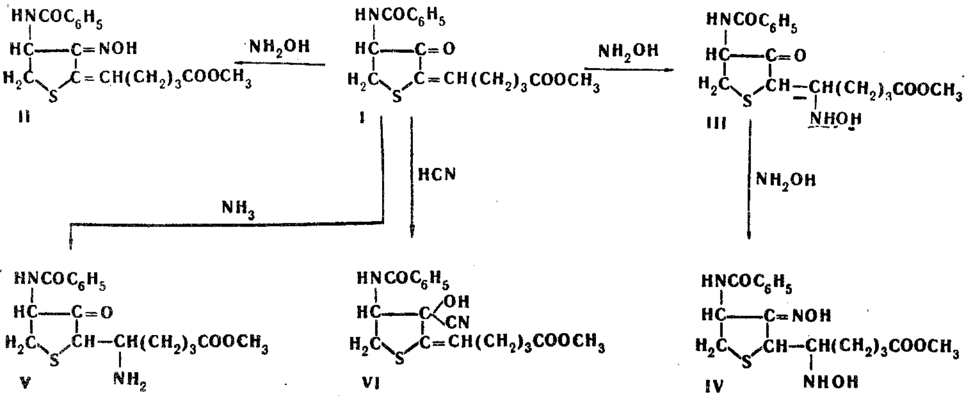
Addition of hydroxylamine, ammonia and hydrocyanic acid to 4-benzoylamino-3-keto-2-(δ-carbomethoxybutylidene)-thiophane and to 4-benzoylamino-3-keto-2-benzylidenethiophane has been investigated. 4-Benzoylamino-3-keto-2-(δ-carbomethoxybutylidene) thiophane participates in a nucleophilic addition reaction both at the carbonyl group, and at the multiple bond, unlike 4-benzoylamino-3-keto-2-benzylidenethiophane, which reacts only at the carbonyl group.

A special feature of the structure of 4-benzoylamino-3-keto-2-(δ-carbomethoxybutylidene) thiophane (I), and 4-benzoylamino-3-keto-2-benzylidenethiophane (VII) is the presence of a conjugated system $-CH=\underset{|}{C}-\underset{|}{C}=O$, formed in the Knoevenagel condensation of 3-ketothiophane and of the corresponding aldehyde. Consequently it was of interest to study the reactions of nucleophilic addition [1-9] of these α, β-unsaturated heterocyclic ketones at both the carbonyl group, and at the multiple bond.

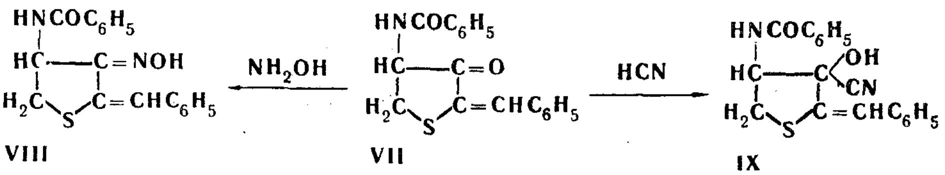
It is known that 4-benzoylamino-3-keto-2-(δ-carbomethoxybutylidene)-thiophane (I) in pyridine adds hydroxylamine at the carbonyl group, to give 4-benzoylamino-3-oximino-2-(δ-carbomethoxybutylidene) thiophane (II) [10]. However, it is shown by us that in aqueous ethanol, in the presence of sodium carbonate, hydroxylamine adds at the multiple bond to give 4-benzoylamino-3-keto-2-(α-hydroxylamino-δ-carbomethoxybutyl)thiophane (III). Compound III and hydroxylamine in pyridine gave, as expected, 4-benzoylamino-3-oximino-2-(α-hydroxylamino-δ-carbomethoxybutyl)thiophane (IV).



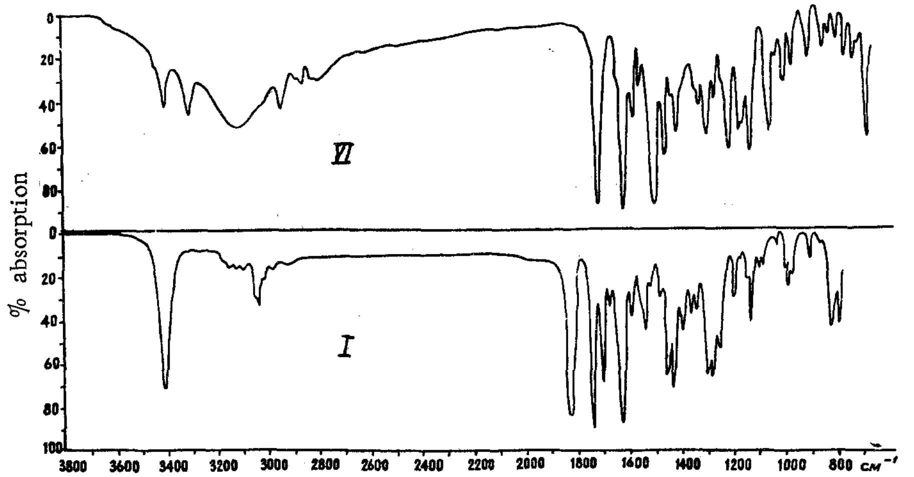
Addition of ammonia could be effected only at the carbon-carbon double bond. The reaction takes place readily, and leads to formation of 4-benzoylamino-3-keto-2-(α-amino-δ-carbomethoxybutyl) thiophane (V).

Hydrogen cyanide adds to compound I only at the carbonyl group, and the direction of addition is unchanged in the basicity of the reaction medium. The IR spectrum of 4-benzoylamino-3-cyano-3-hydroxy-2-(δ-carbomethoxybutylidene) thiophane (VI) shows the presence of a hydroxyl group (frequency 3320 cm^{-1}) (see figure), thus confirming the addition of hydrocyanic acid at the carbonyl group.

4-Benzoylamino-3-keto-2-benzylidenethiophane (VII) [11] undergoes nucleophilic addition only at the carbonyl group, to give 4-benzoylamino-3-oximino-2-benzylidenethiophane (VIII) and 4-benzoylamino-3-cyano-3-hydroxy-2-benzylidenethiophane (IX).



Obviously the presence of an electron-donating phenyl group at the double bond in compound VII enhances its electron density, and so impedes nucleophilic addition at that bond.



IR spectra (measured with a UR-10 instrument and a KBr prism): I) 4-benzoylamino-3-keto-2-(δ-carbomethoxybutylidene) thiophane; VI) 4-benzoylamino-3-cyano-3-hydroxy-2-(δ-carbomethoxybutylidene)-thiophane.

Experimental

4-Benzoylamino-3-oximino-2-(δ-carbomethoxybutylidene)thiophane (II). 12 g 4-benzoylamino-3-keto-2-(δ-carbomethoxybenzylidene) thiophane (I), and 5.0 g hydroxylamine hydrochloride in pyridine [10] gave 6.27 g (50%) compound II. Colorless needles, mp 125-136° (mixture of syn- and anti- forms). Absorption spectrum (in EtOH): λ_{max} 230 mμ (ε 1.98 × 10^4) and 280 mμ (ε 0.97 × 10^4). Found: C 58.40, 58.67; H 5.84, 5.95; S 9.07, 8.90%. Calculated for $C_{17}H_{20}O_4S$: C 58.60; H 5.79; S 9.24%.

4-Benzoylamino-3-keto-2-(α-hydroxylamino-δ-carbomethoxybutyl) thiophane (III). a) 0.15 g hydroxylamine hydrochloride in 1 ml MeOH was mixed with a NaOMe solution prepared from 0.05 g Na and 2 ml MeOH, and products filtered, and the filtrate added to 0.58 g compound I in 4 ml MeOH. The mixture was stirred for 2 hr at 35°, the solvent then removed under reduced pressure, after which the residue was triturated with ether. Yield 0.45 g (71.8%). Colorless plates, mp 128-129° (ex EtOH). Found: C 55.47, 55.60; H 6.04, 6.09; N 8.10, 7.85; S 9.07, 9.08%. Calculated for $C_{17}H_{22}N_2O_5S$: C 55.68; H 6.02; N 7.61; S 8.70%.

b) A solution of 0.13 g hydroxylamine hydrochloride in 1 ml water was added to a solution of 0.50 g compound I in 4 ml MeOH, the whole warmed to 40°, a solution of 0.1 g NaOAc in 1 ml water added, and the mixture stirred for 1 hr at 50°. The alcohol was removed under reduced pressure, the precipitate separated off, and washed with water and ether. Yield 0.49 g (89.2%), mp 128-129° (ex EtOH). Undepressed mixed mp with the compound prepared by method a.

4-Benzoylamino-3-oximino-2-(α-hydroxylamino-δ-carbomethoxybutyl)-thiophane (IV). A mixture of 0.2 g compound III, 3 ml pyridine, and 0.07 g hydroxylamine hydrochloride was held at 30° for 96 hr. The pyridine was evaporated off under reduced pressure, 10 ml $CHCl_3$ added, the solution washed with water and dried. The solvent was distilled off, and 1 ml ether added to the residue. The precipitate was separated off, and washed with ether. Yield 0.12 g (55%); colorless prisms, mp 141-142° (ex EtOH). Found: C 53.58, 53.42; H 5.72, 5.59; N 11.44%. Calculated for $C_{17}H_{23}N_3O_5S$: C 53.53; H 6.08; N 11.08%.

4-Benzoylamino-3-keto-2-(α-amino-δ-carbomethoxybutyl) thiophane (V). NH_3 was passed for 4 hr into a solution of 0.5 g compound I in 20 ml MeOH held at 0° to −3°. Excess NH_3 and solvent were removed under reduced pressure. The residue was dissolved in 2 ml MeOH, and the compound precipitated with ether. Yield 0.3 g (58.2%), colorless plates mp 62° (decomp, ex EtOH). Found: C 58.27, 58.30; H 6.53, 6.50; N 7.72, 7.49; S 8.75, 8.76%.

Calculated for $C_{17}H_{22}N_2O_4S$: C 58.26; H 6.32; N 8.03; S 9.14%.

4-Benzoylamino-3-cyano-3-hydroxy-2-(δ-carbomethoxybutylidene) thiophane (VI). HCN gas was passed for 3 hr into a solution of 0.45 g compound I in 3 ml pyridine held at 0° to −3°. After 12 hr the solvent was removed under reduced pressure, and 1 ml EtOH added to the residue. Yield 0.4 g (82.7%); colorless prisms, mp 136–137° (ex EtOH). Found: C 59.72, 59.65; H 5.71, 5.62; N 7.58, 7.50; S 9.17, 9.10%. Calculated for $C_{18}H_{20}N_2O_4S$: C 59.98; H 5.59; N 7.77; S 8.89%.

4-Benzoylamino-3-oximino-2-benzylidenethiophane (VIII). 0.14 g hydroxylamine hydrochloride was added to 0.5 g compound VII in 6 ml pyridine, the whole held at 30° for 20 hr, then 12 ml water added, and the mixture extracted with $CHCl_3$ (5 times, with 5 ml each time). The $CHCl_3$ extract was made acid to congo red, in the cold, with 2.5 N HCl (about 0.5 ml), then washed with water. On standing, the $CHCl_3$ extracts gave a precipitate. Yield 0.3 g (60%), colorless needles, mp 182.5–183° (decomp, ex dioxane). Found: C 66.48, 66.40; H 5.14, 5.33; N 8.85, 8.96; S 9.88, 10.0%. Calculated for $C_{18}H_{16}N_2O_2S$: C 66.64; H 4.97; N 8.63; S 9.88%.

4-Benzoylamino-3-cyano-3-hydroxy-2-benzylidenethiophane (IX). Prepared similarly to VI, from 0.5 g of that compound. Yield 0.3 g (55.6%); colorless plates. Compound IX readily loses hydrogen cyanide on warming. Found: C 64.93; H 5.05; N 7.88, 8.04%. Calculated for $C_{19}H_{16}N_2O_2S \cdot H_2O$: C 64.41; H 5.11; N 7.82%.

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