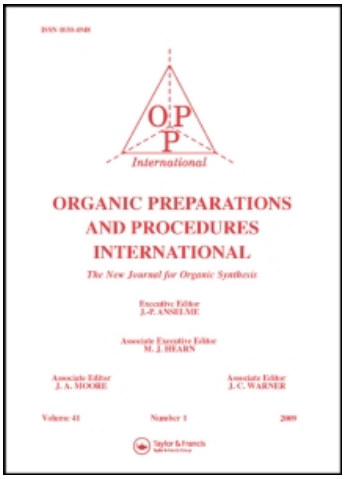

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1-THIA-3-AZACYCLOHEPTANE DERIVATIVES

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1-THIA-3-AZACYCLOHEPTANE DERIVATIVES*

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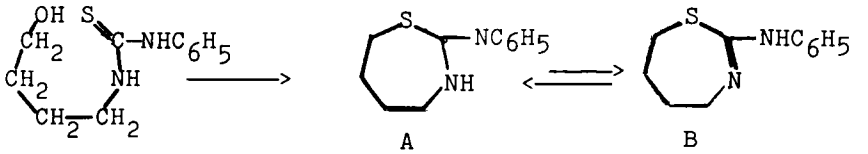
The present paper is a part of our investigations on the preparation of new heterocyclic systems with sulfur and nitrogen in the 1,3-positions using thiourea and its derivatives as starting materials.[1] The formation of 1,3-tetrahydrothiazine derivatives is already known[2-4] and we are now describing the formation of derivatives of a seven-membered ring compound, viz., 1-thia-3-azacycloheptane (II) from N-(1-hydroxybutyl)-N'-phenylthiourea (I).



I A II B

The structure of II with the prevailing form (A) con-

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*Part II of the papers on "Heterocyclic compounds with sulfur and nitrogen." Part I described novel methods of formation of imidazo[2,1-b]thiazole.

taining exo C=N bond was confirmed by the NMR spectrum (Fig. 1) which is similar to that of the analogous 1,3-tetrahydrothiazine examined by Cherbuliez.[6] In addition, its UV

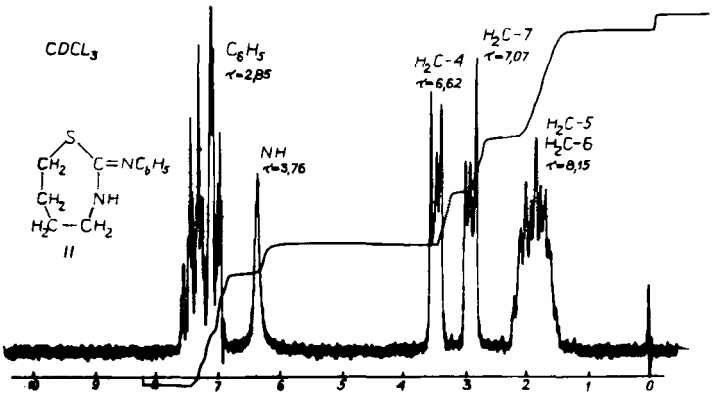
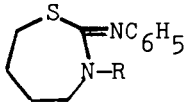


Fig. 1 NMR spectrum of 1-thia-3-azacycloheptane (II)

spectrum λ_{max} = 263 mμ (ε = 8000) confirmed the conjugation of the exo C=N bond with the benzene ring; Tisler[5] found λ_{max} = 263 mμ (ε = 7100) for the analogous 1,3-tetrahydrothiazine.

The infrared spectrum of the starting substance, I showed bands of OH (3400 cm^{-1}), NH (3190 and 1550 cm^{-1}) and aromatic C—C vibrations (1590 cm^{-1}). The product (II) was devoid of the band of OH vibrations and had a new band (1610 cm^{-1}), characteristic of the C=N bond. Derivatives of II were also obtained: 3-benzoyl- (IIa) and 3-thionylanilino-1-thia-3-azacycloheptane (IIb) by the reaction of II with benzoyl chloride and phenyl isothiocyanate respectively.

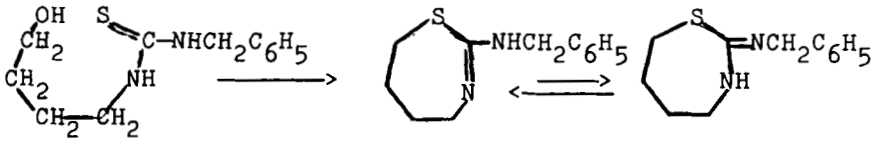


IIa R=C_6H_5CO

IIb R=C_6H_5NHCS

The infrared absorption band, characteristic of the NH vibration was absent and a new band at 1665 cm^{-1} was assigned to C=O vibration of IIa.

The reaction of cyclization was also carried out with *N*-(1-hydroxybutyl)-*N'*-benzylthiourea (III) to yield 2-aminobenzyl-1-thia-3-aza-2-cycloheptene (IV).



III A B IV

The structure of IV with the prevailing form A containing endocyclic C=N bond was confirmed by the NMR spectrum (Fig. 2.) It is similar to NMR spectrum of the analogous Δ^2-dihydro-1,3-thiazine examined by Cherbuliez.[6]

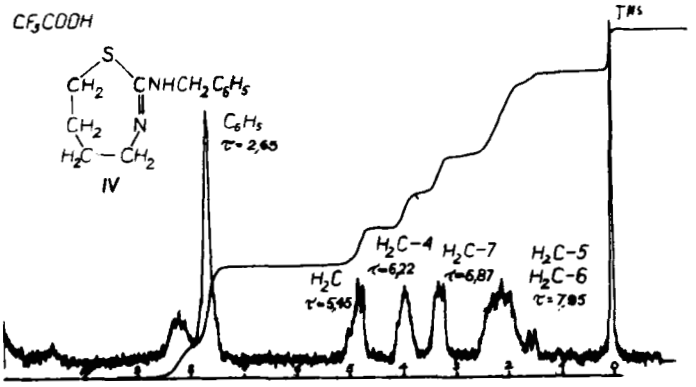


Fig. 2

NMR spectrum of 2-aminobenzyl-1-thia-3-aza-2-cycloheptene (IV)

The infrared spectrum of the N-benzyl analogue IV shows a shoulder at 3150 cm^{-1} (NH vibrations) and a strong band at 1635cm^{-1} (C=N vibration).

EXPERIMENTAL

N-(1-hydroxybutyl)-N'-phenylthiourea (I) was prepared from 4-aminobutanol and phenyl isothiocyanate in ethanol,[7] mp. 104-105°, lit.[7] mp. 104-105°.

2-Phenylimino-1-thia-3-azacycloheptane (II). N-(1-hydroxybutyl)-N'-phenylthiourea (I) 2.2 g. (0.01 mole) was refluxed in 1000 ml. of 6 N hydrochloric acid for 1 hour. The cooled solution was neutralized with solid sodium hydroxide and the product (II) crystallized on standing. It was recrystallized first from 50% aqueous ethanol then from acetone. The yield was 0.5 g. (25%), mp. 129-130°.

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.0; H, 6.8; N, 13.6%, M.W., 206.2.

Found: C, 64.2; H, 6.9; N, 13.1%, M.W., 202 (Rast).

3-Benzoyl-2-phenylimino-1-thia-3-azacycloheptane (IIa). To a suspension of 0.5 g. (2.5 mmoles) of II in a mixture of anhydrous dioxane (6 ml.) and pyridine 0.4 g. (5 mmoles) was added dropwise 0.7 g. (5 mmoles) of benzoyl chloride dissolved in 2 ml. of dioxane. The mixture was warmed to 40° for 3 hours. Upon cooling pyridine hydrochloride precipitated and was filtered, the solution diluted with 25 ml. of cold water. The precipitated product was crystallized from benzene to give 0.7 g. (65%) of IIa, mp. 157-158°.

Anal. Calcd. for $C_{18}H_{18}N_2OS$: C, 69.7; H, 5.9; N, 9.0; S, 10.3%.

Found: C, 69.9; H, 6.0; N, 8.9; S, 10.5%.

3-(Phenylthiocarbamoyl)-2-phenylimino-1-thia-3-azacycloheptane (IIb). Product (II) 0.5 g. (2.5 mmoles) was refluxed with phenylisothiocyanate 0.35 g. (2.5 mmoles) in acetone (10 ml.) for 8 hours and was left to crystallize. The product (IIb) was purified by crystallization from anh. ethanol. The yield was 0.8 g. (80%), mp. 67-68°.

Anal. Calcd. for $C_{18}H_{19}N_3S_2$: C, 63.3; H, 5.6; N, 12.3%.

Found: C, 63.1; H, 5.6; N, 12.2%.

N-(1-hydroxybutyl)-N'-benzylthiourea (III). Benzyl isothiocyanate 7.5 g. (0.05 mole) was dissolved in anh. ethanol (10 ml.) and 4-aminobutanol 4.5 g. (0.05 mole) was added dropwise; heat was evolved. The mixture was left overnight to crystallize. The product was washed with ether and crystallized from ethanol to give 6.8 g. (55%) of (III), mp. 71-72°.

Anal. Calcd. for $C_{13}H_{18}N_2OS$: C, 62.4; H, 7.25; N, 11.2; S, 12.8%.

Found: C, 62.0; H, 7.7; N, 11.3; S, 12.1%.

2-Benzylamino-1-thia-3-aza-2-cycloheptene (IV). Product (III) 2.4 g. (0.01 mole) was refluxed in 1250 ml. 6 N hydrochloric acid for 1 hour. The solution was cooled, neutralized with solid sodium hydroxide and extracted with benzene. The extract was dried over sodium sulfate, the solvent evaporated. The oily product (IV) was crystallized first from aqueous 70%

ethanol then from acetone. The yield was 0.1 g. (5%), mp. 74-75°.

Anal. Calcd. for $C_{12}H_{16}N_2S$: C, 65.4; H, 7.3; N, 12.7%. M.W., 220.3.

Found: C, 65.4; H, 7.5; N, 12.7%. M.W., 220 (Rast).

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