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Abstract

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SYNTHESIS OF ARYL-SUBSTITUTED AZETIDINTHIONES-2

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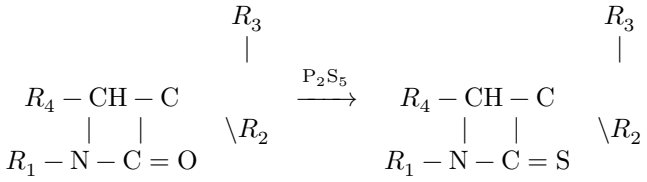
Recently, interest has increased considerably in the synthesis, chemical properties, and biological action of azetidinones-2 (β-lactams). A new contribution to the synthesis of these compounds was made by the work of I. L. Knunyants and N. Gambaryan ([1]), who described a method for obtaining β-lactams from amides of β-chloro-substituted carboxylic acids. E. Testa and co-workers showed the possibility of reducing certain appropriately substituted azetidinones-2 to the corresponding azetidines while retaining the ring ([2]). At the same time, the same group of Italian investigators established the depressant effect of certain aryl-substituted azetidinones-2 on the central nervous system ([3], [4]).

Proceeding from the fact that in some cases replacement of an oxygen atom by sulfur leads to interesting changes both in reactivity and in biological action, we considered it of interest to synthesize certain azetidinthiones-2 and to study their chemical and pharmacological properties. For this purpose we investigated the interaction of various aryl-substituted β-lactams with phosphorus pentasulfide. Provided that the β-lactam ring remains intact, the reaction, as should be expected from the general scheme of the interaction of phosphorus pentasulfide with amides, should lead to formation of the expected β-thiolactams according to the equation:



There are no data in the literature concerning such an interaction of β-lactams with phosphorus pentasulfide, although the preparation of thiolactams with a larger ring by this route is known. Thus, Tafel and Lavachek, by treating pyrrolidone with phosphorus pentasulfide, obtained thiopyrrolidone in 75% yield ([5]).

Our experiments showed that the reaction of aryl-substituted azetidinones-2 with phosphorus pentasulfide does indeed proceed according to the scheme given

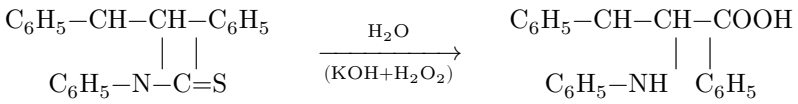
above and leads smoothly to the corresponding azetidinthiones-2 in good yields. In the present work the following azetidinones were investigated:

	R_1	R_2	R_3	R_4	Yield of azetidinthione-2
I	C_6H_5	H	H	C_6H_5	55%
II	C_6H_5	C_6H_5	C_6H_5	H	58%
III	*o*-$CH_3OC_6H_4$	H	C_6H_5	C_6H_5	55%
IV	C_6H_5	H	C_6H_5	C_6H_5	65%

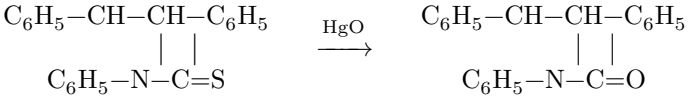
In all the β-lactams investigated, the nitrogen atom is bonded to a phenyl radical. The positions of the remaining aryl substituents were selected so that the 3- or 4-position in the ring remains free or is substituted by one phenyl radical. One of the azetidinones-2 investigated is substituted by two phenyl residues at the carbon atom in the third position.

According to some literature data, rings of these types of β-lactams are comparatively more stable [(6)].

The structure of the azetidinethiones-2 obtained, in addition to the data of elemental analysis, was also proved by alkaline hydrolysis of 1,3,4-triphenylazetidinethione-2 (IV) to α,β-diphenyl-β-phenylaminopropionic acid:



and also by its desulfurization to the initial 1,3,4-triphenylazetidinone-2 with yellow mercuric oxide:



We carried out the interaction of β-lactams with phosphorus pentasulfide in benzene, toluene, or xylene medium with more or less prolonged heating of the mixture (3–15 hr). Isolation of the azetidinethiones-2 obtained presents no particular experimental difficulties. The azetidinethiones-2 obtained by us are almost colorless crystalline substances with melting points lower than those of the initial azetidinones-2. All the azetidinethiones-2 obtained give the qualitative reaction for a thioamide group described by one of us [(7)], consisting in

identification of the hydrogen sulfide evolved on heating the substance under study with hydrazine hydrate in alcoholic solution.

We shall continue our investigations with the aim of obtaining certain other arylated and alkylated azetidinethiones-2 in the ring and of studying their chemical properties and biological action.

Experimental Part

1,4-Diphenylazetidinethione-2 (I). A mixture of 1.15 g (about 0.005 g-mole) of 1,4-diphenylazetidinone-2 and 1.0 g of phosphorus pentasulfide in 40 ml of benzene was heated for 9 hr. The hot transparent solution was decanted and evaporated to dryness. The crude fine-crystalline product was recrystallized from absolute alcohol. M.p. 120–122°. Yield 0.65 g (55%). After repeated recrystallization, m.p. 121–122.5° was determined.

$C_{15}H_{13}NS$ (239.3).	Found %:	N 5.69
	Calculated %:	N 5.86

1,3,3-Triphenylazetidinethione-2 (II). A solution of 1.50 g (about 0.005 g-mole) of 1,3,3-triphenylazetidinone-2 in 20 ml of xylene with 1 g of phosphorus pentasulfide was heated at reflux. After 15 hr the transparent hot solution was decanted and evaporated to dryness without heating. The oil formed crystallized on trituration with a small amount of alcohol. The crude crystalline product was filtered off with suction and recrystallized from absolute alcohol (activated carbon). Yield 0.92 g (58%). After repeated recrystallization, m.p. 115–118.5° (m.p. on a Kofler microscope 116–118.5°).

$C_{21}H_{17}NS$ (315.4).	Found %:	N 4.49
	Calculated %:	N 4.44

1-(o-Methoxyphenyl)-3,4-diphenylazetidinethione-2 (III). A solution of 1.65 g (0.005 g-mole) of 1-(o-methoxyphenyl)-3,4-diphenylazetidinone-2 in 50 ml of a xylene–toluene mixture (1:1) was heated at reflux for 6 hr with 1 g of phosphorus pentasulfide. The hot solution was filtered and the filtrate evaporated to dryness. The resulting yellowish oil was treated with ethyl acetate while being triturated. After evaporation of the ethyl acetate there remained a crystalline product, which was recrystallized from absolute alcohol (acti-

charcoal). Yield 0.95 g (55%). After repeated recrystallization, m.p. 99.5–101°.

$C_{22}H_{19}ONS$ (345.5).	Found, %:	N 4.06
	Calculated, %:	N 4.00

1,3,4-Triphenylazetidinethione-2 (IV). A solution of 3.00 g (0.01 g-mole) of 1,3,4-triphenylazetidinone-2 in 100 ml of xylene with 4.50 ml of phosphorus

pentasulfide was heated at boiling for 3 h. The hot solution was filtered and the filtrate was evaporated to dryness. The remaining oily product was triturated with several milliliters of ethyl acetate. The yellow crystals that formed were recrystallized from absolute alcohol (activated charcoal). M.p. 122–125°. Yield 2.05 g (65%). After repeated recrystallization, m.p. 124–126.5°.

$C_{21}H_{17}NS$ (315.4).	Found, %:	C 79.45; H 5.41; N 5.10; S 10.66
	Calculated, %:	C 79.96; H 5.43; N 4.44; S 10.50

Hydrolysis of 1,3,4-triphenylazetidinethione-2. 0.70 g of 1,3,4-triphenylazetidinethione-2 was suspended in 30 ml of a 10% solution of potassium hydroxide (25% alcoholic solution), and the suspension was heated at gentle boiling until complete dissolution, which occurs in 8 h. The hot solution was filtered; 2 ml of hydrogen peroxide was added to the filtrate, and it was stirred and left at room temperature overnight. The flocculent precipitate that formed was filtered off; the filtrate was acidified with dilute acetic acid and extracted with ether. The residue obtained after evaporation of the ether was recrystallized from an alcohol–water mixture (activated charcoal). M.p. 157–158°. A mixed sample with α,β-diphenyl-β-phenylaminopropionic acid having the same melting point gives no melting-point depression.

Desulfurization of 1,3,4-triphenylazetidinethione-2. A mixture of 0.50 g of 1,3,4-triphenylazetidinethione-2 and 1 g of yellow mercuric oxide in 25 ml of alcohol and 2 ml of water was heated at gentle boiling with constant stirring for 2 h. The suspension gradually turned black. The hot mixture was filtered through a dense filter; the precipitate on the filter was washed with several milliliters of hot alcohol, and the filtrate was evaporated to dryness on a water bath. The resulting grayish product was recrystallized from alcohol (activated charcoal). The purified substance has m.p. 132–133.5° and, with 1,3,4-triphenylazetidinone-2, gives no depression of the melting point.

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Note: Figure translations are in progress. See original paper for figures.