INDOLE DERIVATIVES

LXXIV.* SYNTHESIS OF INDOLE ANALOGS OF CEPHALOSPORIN

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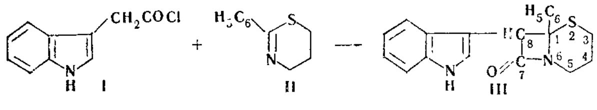
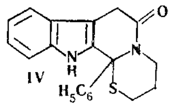
The reaction of 3-indolylacetyl chloride with 2-phenyl-5,6-dihydro-1,3-thiazine and cyclohexanone anil in the presence of triethylamine was used to synthesize 6-aza-2-thia-8-(3-indolyl)-1-phenylbicyclo[4.2.0]-7-heptanone and cyclohexanespiro-2-[1'-phenyl-3'-(3-indolyl)-4'-azetidinone].

In a continuation of the research in [2] on the synthesis of β-lactams in the indole series, we studied the possibility of obtaining 2-azetidinone derivatives containing an indole residue in the 3 position. For this, we investigated the reaction of 3-indolylacetyl chloride with several Schiff bases. 3-Indolylacetyl chloride (I) reacts with benzylideneaniline in the presence of triethylamine to give a mixture of cis and trans isomers of the corresponding β-lactams [2].

It seemed of interest to use this reaction for the synthesis of the indole analog of cephalosporin. For this, we studied the reaction of 3-indolylacetyl chloride (I) with 2-phenyl-5,6-dihydro-1,3-thiazine (II) in the presence of triethylamine, which led to the formation of 6-aza-2-thia-8-(3-indolyl)-1-phenylbicyclo-[4.2.0]-7-heptanone (III).




IV

The order of the addition of the reagents has a substantial effect on the results of the reaction. Thus the β-lactam is formed when I is added to a mixture of thiazine II and triethylamine, while the reaction products could not be identified when triethylamine was added to a mixture of I and II. The structure of lactam III was confirmed by IR and PMR spectroscopy. There are absorption bands at 3350 cm^{-1} (indole NH) and 1760 cm^{-1} (β-lactam C = O) in the IR spectrum. A singlet at δ 5.10 (7-CH) and several multiplets at 1.84 (3-CH$_2$), 2.6 (2-CH$_2$), and 4.3 ppm (4-CH$_2$) were noted in the PMR spectrum (CDCl$_3$), which confirms the presence of a thiazan ring. The signal at 6.64 ppm is due to the proton in the α position of the indole ring. The presence of this signal makes it possible to reject structure IV for the compound obtained.

Up to now, spiro-β-lactams have received very little study [3], and it was therefore of interest to obtain a spiro-β-lactam containing an indole ring. For this, we carried out the reaction between 3-indolylacetyl chloride (I) and cyclohexanone anil (V). The reaction gave a mixture from which cyclohexanespiro-2'-[1'-phenyl-3'-(3-indolyl)-4'-azetidinone] (VI) could be isolated. The presence of an absorption band at 1735 cm^{-1} in the IR spectra makes it possible to choose from structures VI, VII, and VIII and to assign the β-lactam structure (VI) to the compound obtained. Compound VI is only slightly soluble in the usual solvents, and its PMR spectrum therefore cannot be recorded.

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*See [1] for communication LXXIII.

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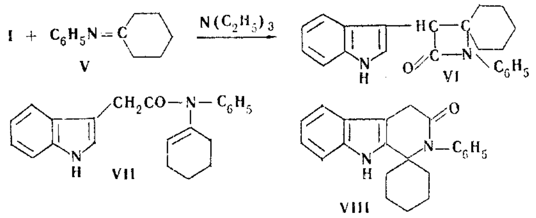

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrometer, and the PMR spectra were recorded with a JNM-4H-100 spectrometer.

6-Aza-2-thia-8-(3-indolyl)-1-phenylbicyclo[4.2.0]-7-heptanone (III). A solution of 1.9 g (0.01 mole) of 3-indolylacetyl chloride [4] in 60 ml of dry methylene chloride was added dropwise with stirring to a solution of 1.7 g (0.01 mole) of 2-phenyl-5,6-dihydro-1,3-thiazine (II) [5] and 1.5 ml (0.01 mole) of triethylamine in 50 ml of dry methylene chloride at 0-5°. The mixture was stirred for another 2 h and allowed to stand overnight at room temperature. The solution was washed with water and dried over sodium sulfate. The solvent was removed by distillation, and the residual viscous mass was washed with ether. The resulting product was dissolved in methylene chloride. The solution was introduced into a column packed with neutral aluminum oxide and eluted successively with methylene chloride and a mixture of methylene chloride and alcohol (6 : 1). The solvents were removed by vacuum distillation, and the residue was recrystallized from aqueous acetone to give 0.7 g (21%) of a product with mp 187-189°. IR spectrum ($CHCl_3$): 1760 cm^{-1} (β-lactam C = O). Found: C 72.1; H 5.7; N 8.7; S 9.1%. $C_{10}H_{18}N_2OS$. Calculated: 71.9; H 5.4; N 8.4; S 9.6%.

Cyclohexanespiro-2'-[1'-phenyl-3'-(3-indolyl)-4-azetidinone] (VI). Compound VI was similarly obtained by the reaction of cyclohexanone anil (V) with 3-indolylacetyl chloride in the presence of triethylamine. The reaction mixture was chromatographed on neutral aluminum oxide with elution by methylene chloride to give 10% of a product with mp 226° (dec., from aqueous acetone). IR spectrum ($CHCl_3$): 1735 cm^{-1} (β-lactam C = O). Found: C 79.8; H 6.6; N 8.4%. $C_{22}H_{22}N_2O$. Calculated: C 80.0; H 6.7; N 8.5%.

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