SYNTHESIS OF 1-ALKYL(ARALKYL)-4-ACYL-2-PIPERAZINONES

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1-Alkyl(aralkyl)-4-acyl-2-piperazinones are formed in high yields during selective acylation of N-monosubstituted ethylenediamines by benzoyl and cyclohexylcarbonyl chlorides in the presence of pyridine hydrochloride and treatment of the reaction products with chloroacetyl chloride in the presence of potassium tert-butylate.

Among 2-piperazinones, having different biological activities [1-3], the little investigated 4-acyl derivatives are of special interest, since the 4-acyl-2-piperazinone fragment is included in the structure of a new anthelmintic prasiquantel (I) [4] with a broad spectrum of activity. The aim of the present work was to find a suitable method for the synthesis of 1-alkyl(aralkyl)-4-acyl-2-piperazinones (IIa-g). Compounds IIa-g were selected as the object products, since they contain the same functional groups as prasiquantel, and have a similar lyophilicity.

In the course of the investigation, we studied schemes of synthesis of compound IIa-g, based on the use of available N-monosubstituted ethylenediamines IIIa-c.

Taking compound IIIa as an example, we first studied the variant of the synthesis of 2-piperazinones, which gives the formation of a hetero ring by the cyclization of the bis-chloroacetyl derivative IV by the action of a strong base, and the subsequent elimination of the chloroacetyl group.

During the acylation of compound IIIa by chloroacetyl chloride, the derivative IV is obtained in high yield. By the action of potassium tert-butylate, this converts into piperazinone IIh in a yield of 37% only. Even mild acidic hydrolysis of compound IIh results not...
only in splitting of the chloroacetyl group, but also in opening of the piperazine ring. As the result, amino acid V is formed, which has been previously obtained by another method [5]. Because of this, specific methods were used for the removal of the chloroacetyl group: action of o-phenylenediamine [6] or thiourea [7] on compound IIh. In both cases pyrazinone VI was obtained from compound IIh in a yield not higher than 55-60%, since the isolation of the reaction products is difficult, due to the presence of difficultly separable impurities. The acylation of compound IIh by benzoyl of 4-nitrobenzoyl chloride leads to compounds IIIa,b.

Better results were obtained by the alternative route also based on the use of substituted ethylenediamines IIIa-c. The latter contain both a primary and secondary amino group, differing in the degree of steric hindrance. It could be assumed that the less hindered primary amino group will be preferentially acylated. However, only in the case of compound IIIc, where the differences in the environment of the amino groups are in particular considerable, it is possible under normal conditions (see the Experimental section) to acylate selectively the primary group and to obtain compounds VIIa,b. N-Benzyl-N,N'-dibenzoylethlenediamine (VIII) is formed under these conditions from equimolar amounts of ethylene-diamine IIIa and benzoyl chloride, and ~50% of the initial compound IIIa, which does not enter the reaction, is left. Monoacylation of compounds IIIa,b could be accomplished using a method previously proposed for 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline [8]. The reaction of ethylenediamines IIIa,b with benzoyl or cyclohexylcarbonyl chloride in acetonitrile in the presence of pyridine hydrochloride leads to compounds VIIc-f in high yields.

The secondary amino group becomes acylated by the action of chloroacetyl chloride on acetylethlenediamines VIIa-f in the presence of potassium tert-butyrate, and this is followed by cyclization to give piperazinones IIIa,c-g. The 4-acyl-2-piperazinones IIa-g thus synthesized are colorless crystalline substances, an exception being compound IIh, which is a viscous liquid. The structure of the compounds was confirmed by elemental analysis and IR spectroscopy (Table 1).

Thus, the selective acylation of N-monosubstituted ethylenediamines and subsequent reaction with chloroacetyl chloride in the presence of potassium tert-butylate represents a convenient general method for the synthesis of 4-acyl-2-piperazinones.

**EXPERIMENTAL**

The IR spectra of the compounds synthesized were run on a UR-20 spectrophotometer in KBr tablets. The course of the reactions and the purity of the products obtained controlled by TLC on Silufol plates in 3:1 ether-acetone system.

Compounds IIIa,b were obtained from ethylenediamine and the corresponding aralkyl chloride by the method in [9], and compound IIIc by reducing a-ethylaminobenzyl cyanide with lithium aluminum hydride according to a method described in [10].

N-Benzyl-N,N'-bis(chloroacetyl)ethylenediamine (IV). A solution of 15.5 ml (200 mmoles) of chloroacetyl chloride in 10 ml of methylene chloride is added in the course of 20 min, at 0°C to a mixture of 13.5 g (90 mmoles) of compound IIIa and 30 g (280 mmoles) of Na₂CO₃ in 100 ml of anhydrous methylene chloride. The mixture is stirred for another 40 min, the precipitate is filtered, and washed with 100 ml of methylene chloride. The filtrates are combined and evaporated in vacuo. Yield, 25.2 g (92%) of compound IV in the form of a pale-yellow oil. IR spectrum: 3330 (NH), 1665 (CO), 1645 cm⁻¹ (sh, CO). Compound IV is used in the following stage without additional purification.

1-Benzyl-4-chloroacetyl-2-piperazinone (IIh). A solution of potassium tert-butylate, prepared from 0.274 (7 mmoles) of potassium and 10 ml of tert-butanol, is added in the course of 20 min to a solution of 2.02 g (7 mmoles) of compound IV in 20 ml of anhydrous tert-butanol. The mixture is stirred for another 20 min, 100 ml of water are added, and the mixture is ex-