INDOLE DERIVATIVES

CXII.* SYNTHESIS OF 1-BENZOYL-3-BENZAMIDO-3-(3-INDOLYLMETHYL)-PYRROLIDINE-2,4-DIONE BY ALKYLATION OF 2-PHENYL-5-OXAZOLONE WITH GRAMINE METHYLMETHOSULFONATE

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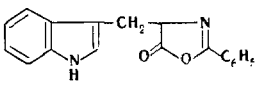
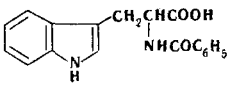
1-Benzoyl-3-benzamido-3-(3-indolylmethyl)pyrrolidine-2,4-dione was obtained instead of an alkylation product in the alkylation of 2-phenyl-5-oxazolone with gramine methylmethosulfonate. The reaction proceeds via initial autocondensation of the oxazolone under the influence of sodium hydride to give 1-benzoyl-3-benzamidopyrrolidine-2,4-dione. Alkylation of the latter with gramine methylmethosulfonate leads to 1-benzoyl-3-benzamido-3-(3-indolylmethyl)-pyrrolidine-2,4-dione, the alkaline hydrolysis of which gave 3-benzamido-3-(3-indolylmethyl)-pyrrolidine-2,4-dione.

Up until recently, there was no information in the literature regarding the alkylation reactions of 2-phenyl-5-oxazolone (I) (azlactone). In 1974 an attempt was made to alkylate the azlactone with benzyl halides in order to obtain amino acids [2]; this attempt led to the usually undesired products of dialkylation of hippuric acid.

In order to synthesize tryptophan we made an attempt to alkylate azlactone I with gramine methylmethosulfonate (I) in dimethyl sulfoxide (DMSO) in the presence of sodium hydride. Two substances, which, according to the results of elementary analysis and the mass spectral data could not have the structures of products of alkylation of the azlactone (III) or of hydrolysis of the latter – the corresponding hippuric acid – were obtained when the reaction mixture was maintained at 20°C for 12-15 h.



III



IV

The first compound has a doubled (with respect to the azlactone) molecular weight (322 by mass spectrometry) and an enol hydroxyl group (positive reaction with $FeCl_3$) and does not contain an indole ring. The UV spectra of this compound and the azlactone differed markedly from one another (Fig. 1). This substance vanishes when the reaction time in the alkylation of the azlactone is increased to 48 h, and it is converted to the second compound, which we obtained directly from the azlactone, in the case of alkylation with methylsulfosulfonate II under similar conditions. The second substance does not give a coloration with $FeCl_3$ and, according to the mass and PMR spectral data, contains an indole ring. The UV spectra of the two substances isolated from the reaction are similar to one another (Fig. 1).

We established that a substance with mp 138° that does not contain an indole ring is obtained from the azlactone in DMSO in the presence of sodium hydride and thus is the product of autocondensation of the oxazolone.

According to the literature data, a substance with a molecular weight of 322 and mp 138° was obtained from hippuric acid [3] and its derivatives, including the azlactone [4]. The problem of its structure was dis-

*See [1] for communication [1].

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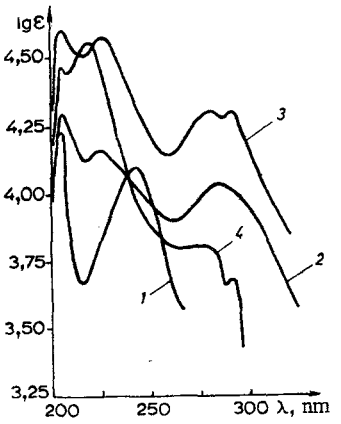
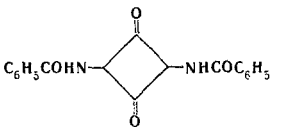
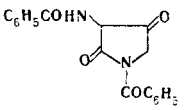


Fig. 1. UV spectra (in alcohol): 1) I; 2) VI; 3) VIII; 4) IX (c 10^{-5} M).

cussed but remained unsolved [5, 6]. Rugheimer, who was the first to obtain this compound [3], proposed a cyclobutanedione derivative structure (V) or a pyrrolidine-2,4-dione structure (VI) for it, and regarded the latter structure as being the most likely one.



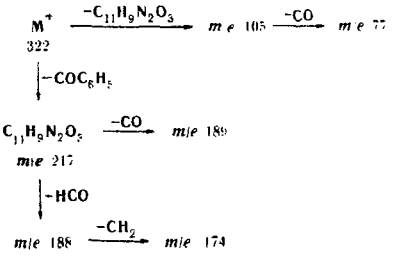
V



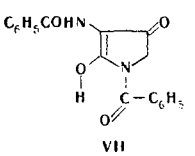
VI

An attempt by Cornforth and Huang [6] to prove the structure of this compound by "alternative" synthesis from 3-benzamidopyrrolidine-2,4-dione was unsuccessful. Cyclobutanedione structure V could not be rejected for it.

The compound with mp 138° that we synthesized was found to be identical to Rugheimer's substance, which we also obtained by "alternative" synthesis. An examination of the mass and PMR spectra of this compound solves the problem of its structure in favor of structure VI. Its mass spectrum contains a rather intense molecular ion peak with a mass of 322. The maximum peak in the spectrum is the peak of a fragment ion with m/e 105, which confirms the presence of a benzoyl fragment. The peaks of fragment ions with masses of 217, 189, 188, 174, and 77 are somewhat less intense.



According to the PMR spectra of solutions in $CDCl_3$, C_5D_5N, CF_3COOD, and d_6-DMSO, the compound has the structure of an intramolecular chelate (VII). The signal of the protons of the CH_2 group is observed

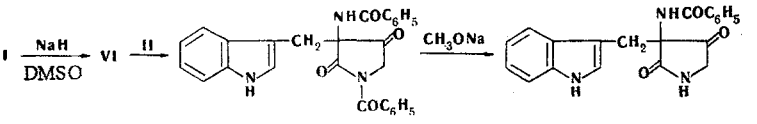


VII

as a singlet at 4.48 ppm (in $CDCl_3$). The multiplets at 7.25–7.95 ppm correspond to the protons of phenyl rings; the signals of the NH and OH protons are broad singlets at 8.05 and 12.57 ppm, respectively.

The IR spectrum of VII contains the broad band of associated OH bonds at 2300-2700 cm^{-1} that is characteristic for the enol form of β-diketones.

On the basis of the mass and PMR spectra in d_6-DMSO, as well as the above-indicated data, the product that we isolated in the alkylation of the azlactone with methylmethosulfonate II has a 1-benzoyl-3-benzimidazo-3-(3-indolylmethyl)pyrrolidine-2,4-dione structure (VIII).



VIII IX

The mass spectrum of VIII does not contain a molecular ion peak, but the peaks of fragment ions with masses of 321, 216, 105, and 77 confirm the presence of a substituted pyrrolidine ring, the fragmentation of which proceeds in the same way as in the case of VI. In addition, there are peaks with masses of 130, 129, 128, and 103, which confirm the presence in the compound of a 3-indolylmethyl grouping.

Thus the impossibility of obtaining a product of alkylation of the azlactone in this case is associated with the case of its autocondensation to give VI, which subsequently is alkylated by methylmethosulfonate II.

Like VI, in alkaline media skatylpyrrolidinedione VIII retains its cyclic structure, losing only the benzoyl group and undergoing conversion to IX.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of 10^{-5} M alcohol solutions of the compounds were recorded with an SF-4 spectrophotometer. The PMR spectra of the compounds were recorded with a JNM-MH-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 50 eV and a cathode emission current of 1.5 mA.

Alkylation of 2-Phenyl-5-oxazolone with Gramine Methylmethosulfonate. A suspension of 0.03 g (1.5 mmole) of sodium hydride in mineral oil was added to a solution of 0.24 g (1.5 mmole) of 2-phenyl-5-oxazolone in 15 ml of DMSO, and the mixture was stirred and treated with 0.45 g (1.5 mmole) of gramine methylmethosulfonate and allowed to stand at room temperature for 12-15 h. It was then diluted with water and acidified to pH ~ 3-4 with 5% HCl solution. The precipitate was removed by filtration and washed successively with water (the aqueous filtrate was allowed to stand) and alcohol–petroleum ether to give 0.24 g (71%) of dibenzoyl derivative VIII with mp 241-242° (from alcohol). PMR spectrum (d_6-DMSO): δ 3.43 and 4.32 (J ≈ 18 Hz, q, pyrrolidine ring CH_2), 3.46 and 3.54 (J ≈ 14 Hz, q, skatyl CH_2); 6.85-7.85 (m, aromatic protons), 9.28 and 10.75 ppm (s, NH). IR spectrum, ν, cm^{-1}: 1550 s, 1590 m (CONH), 1630 s, 1705 (CON <), 1745 (C=O), 2600-2800 w (associated OH), 3080 m, 3290 s br (NH), and 3380 s (indole NH). Found: C 72.0; H 4.9; N 9.3%. $C_{27}H_{21}N_3O_4$. Calculated: C 71.8; H 4.7; N 9.3%.

The aqueous filtrate was extracted with ether and ethyl acetate, and the ether extracts were combined, washed with water, dried with $MgSO_4$, and evaporated to give an oil, which crystallized on standing or when petroleum ether was added. The yield of VI was 0.05 g (24%). Crystallization of VI from alcohol gave the hydrate with mp 85-87°. Found: C 65.2; H 4.6; N 8.4%. $2C_{18}H_{14}N_2O_4 \cdot H_2O$. Calculated: C 65.3; H 4.5; N 8.5%. A product with mp 138-139° [3] was obtained after the hydrate was dried in vacuo at 60° for 10-12 h. No melting-point depression was observed for a mixture of this product with a sample obtained by the method in [4]. IR spectrum ν, cm^{-1}: 1560 s, 1580 m (CONH), 1610 m, 1675 s (CON <), 1720 (C=O), 2600-2750 br w (associated OH), 3080 m, 3380 br m, and 3500 br m (NH). Found: C 67.3; H 4.5; N 8.7%; M 322 (mass spectrometrically). $C_{18}H_{17}N_2O_4$. Calculated: C 67.1; H 4.4; N 8.7%.

1-Benzoyl-3-benzamido-3-(3-indolylmethyl)pyrrolidine-2,4-dione (VIII). A) This compound was obtained from 0.2 g (1.2 mmole) of 2-phenyl-5-oxazolone, 0.02 g (1.2 mmole) of sodium hydride (suspension in oil), and 0.31 g (1.2 mmole) of gramine methylmethosulfonate in 15 ml of DMSO by the method described above. The reaction time was 48 h, and the yield was 0.25 g (91%).

B) A 0.49-g (73%) sample of VIII was similarly obtained from 0.48 g (1.5 mmole) of pyrrolidinedione VI, 0.03 g (1.5 mmole) of sodium hydride (suspension in oil), and 0.45 g (1.5 mmole) of gramine methylmethosulf-

onate in 20 ml of DMSO, the reaction time was 12 h and the product had mp 241-243° (from alcohol). No melting-point depression was observed for a mixture of this product with VIII obtained from 2-phenyl-5-oxazolone.

1-Benzoyl-3-benzamidopyrrolidine-2,4-dione (VI). This compound was obtained from 0.24 g (1.5 mmole) of 2-phenyl-5-oxazolone and 0.03 g (1.5 mmole) of sodium hydride (suspension in oil) in 15 ml of DMSO in analogy with the method presented above. Workup gave 0.2 g (83%) of a product with mp 137-138° after drying in vacuo at 60-70° for 10 h. No melting-point depression was observed for a mixture of this product with VI obtained by alkylation of azlactone I.

3-Benzamido-3-(3-indolylmethyl)pyrrolidine-2,4-dione (IX). A 0.25-g (0.55 mmole) sample of pyrrolidinedione VIII was dissolved in 15 ml of absolute methanol to which 1 mg of sodium metal had previously been added, and the mixture was allowed to stand at room temperature overnight. The resulting solution was acidified to pH ~ 4-5 with 5% hydrochloric acid, and the excess alcohol was evaporated until the product began to crystallize. The precipitate was removed by filtration and washed with aqueous alcohol to give 0.17 g (89%) of IX with mp 252-253° (from aqueous alcohol). PMR spectrum (C_5D_5N), δ: 3.05 and 4.08 (J = 17.2 Hz, q, pyrrolidine ring CH_2), 3.75 and 3.94 (J = 13 Hz, skatyl CH_2), 6.95-8.10 (m, aromatic protons), 9.00, 10.07, and 11.72 (s, NH). IR spectrum, ν, cm^{-1}: 1540 s, 1580 m (CONH–), 1600 m, 1635 s (CON<), 1710-1720 s, 1780 m (C=O), 2600-2800 w (associated OH), 3080 m, 3270-3350 br s (NH), and 3420 m (indole NH). Found: C 68.8; H 5.2; N 12.3%. $C_{20}H_{17}N_3O_3$. Calculated: C 69.2; H 4.9; N 12.1%.

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