CONDENSATION OF ACETANILIDES WITH N-METHYLOLPYRROLIDONE

Kh. Shakhidoyatov, A. Irisbaev, and Ch. Sh. Kadyrov

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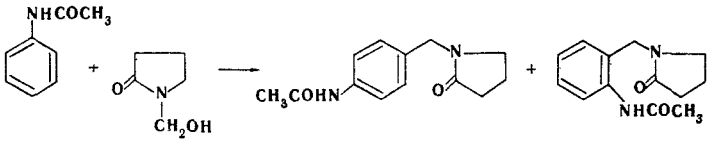
Acetanilides undergo amidomethylation with N-methylolpyrrolidone to give the corresponding N-benzylpyrrolidones.

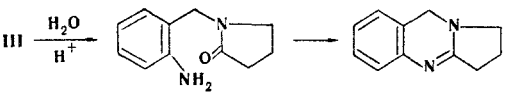
The amidomethylation of 4-nitrotoluene and 4-nitro-1,3-xylene by means of formaldehyde and pyrrolidone or valerolactam has been described [1].

We had hoped that the reaction of acetanilides with N-methylolpyrrolidone (I) would lead to substituted o-acetamidobenzylpyrrolidones, the hydrolysis products of which might cyclize to desoxypeganine (2,3-trimethylene-3,4-dihydroquinazoline) derivatives. With this end in mind, we studied the reaction of acetanilides, o-, m-, and p-acetotoluidines, o-, and p-acetohydroxyacetanilides, p-nitroacetanilides, and 2-acetamidonaphthalene with lactam I in the presence of sulfuric acid. We found that acetanilide reacts with I at 20-70°C. Practically only p-acetamidobenzylpyrrolidone (II), from which we were unable to obtain a disubstitution product, i.e., 2,4-bis(pyrrolidonylmethylene)acetanilide, by the action of excess lactam I, is formed at room temperature and reagent ratios of 1:1 or 1:2.



I II III

When acetanilide is heated to 70° with I, a mixture of ortho and para isomers of II and III is formed in a ratio of 1:8. Hydrolysis of lactam III gives o-aminobenzylpyrrolidone (IIIa), which is cyclized to 2,3-trimethylene-3,4-dihydroquinazoline (IV) on treatment with dehydrating agents.



IIIa IV

The formation of 5-acetamido-2-methylbenzylpyrrolidone (VI) and 2-acetamido-5-methylbenzylpyrrolidone is possible in the case of p-acetotoluidine (V). Only VI was obtained both at room temperature and on heating to 70° for 1 h. The literature contains contradictory data regarding the amidomethylation of amide V. Thus the aromatic ring hydrogen in the 2 and 3 positions with respect to the acetamido group is replaced in the reaction of N-methylolphthalimide with V [2], whereas N,N'-methylenebisacetamide reacts with V to give only N-(2-acetamido-5-methylbenzyl)acetamide [3]; some investigators have not determined the position of the amidomethylene group at all [4, 5].

The mass spectrum of VI contains intense peaks of ions with m/e 161 (74%; ion A) and 119 (100%; ion B). Ion A is apparently formed as a result of detachment of pyrrolidone. Inasmuch as the peaks of an ion with m/e 147, which corresponds to M − 85, are absent in

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the mass spectra of o- and p-acetamidobenzylpyrrolidones IIa and III, it is reasonable to assume that hydrogen is detached from the methyl group. The mass spectrum of the deutero analog (60% enrichment with respect to N—H) of VI contains an ion peak with m/e 162, which also indicates detachment of hydrogen from the methyl group.

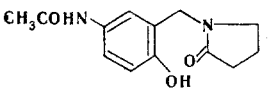
Hydrolysis of amide VI gives the corresponding imine, which is resistant to the action of dehydrating agents. If the pyrrolidonylmethylene group were in the ortho position with respect to the amino group, 6-methyl-2,3-trimethylene-3,4-dihydroquinazoline should have been easily obtained by detachment of water. On the basis of everything set forth above, as well as with allowance for the PMR spectrum, in which an 3-H doublet (6.91 ppm) and an 5-H and 6-H multiplet (7.22 ppm) are observed, the structure of VI can be considered to be established. The optimum sulfuric acid concentration for amidomethylation is 95%; the use of 80, 90, and 98% sulfuric acid lowers the yields of VI to 16, 16, and 10%, respectively.

The amidomethylation of o- and m-acetotoluidines gives, respectively, 2-methyl-4-acetamidobenzylpyrrolidone (VIII) and 2-methyl-3-acetamidobenzylpyrrolidone (IX).

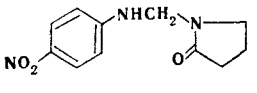
The mass spectra of VIII and IX contain an intense ion peak with m/e 161, which is similar to ion A in the spectrum of VI. The IR spectra of VI and VIII contain absorption bands at 800-815 and 870-890 cm^{-1}, which correspond to 1, 2, and 4 substitution. A multiplet at 6.9-7.3 ppm, which is characteristic for 1,2,3-substituted benzene rings, is observed in the PMR spectrum of IX in the aromatic-proton region.

5-Acetamido-2-hydroxybenzylpyrrolidone (X) was obtained in 33% yield by amidomethylation of p-acetoxyacetanilide with lactam I. A 4-H doublet (6.64 ppm) and a 6-H and 7-H multiplet (7.19 ppm) are observed in the PMR spectrum of X.

Compounds VIII-X are hydrolyzed to amines, and the latter do not undergo cyclization to the corresponding 2,3-trimethylene-3,4-dihydroquinazolines on treatment with dehydrating agents; this is also an indirect confirmation of their structure, repudiating alternative structures.



X



XI

The formation of X can be explained by initial hydrolysis of the acetoxy group of p-acetoxyacetanilide to p-acetamidophenol, which then reacts with N-methylolpyrrolidone. We were unable to isolate a product from the reaction of o-acetamidophenol with I; the starting reagent is hydrolyzed to p-aminophenol.

p-Nitroaniline reacts with lactam I at temperatures below 15° and gives a product of amidoaklylation at the nitrogen atom of XI. Protection of the amino group by means of an acetyl residue does not lead to the desired result: the starting p-nitroacetanilide is recovered at room temperature, and XI is formed when a mixture of the reagents is heated. Product XI was identified by means of its PMR spectrum (multiplet at 6.61 and 7.85 ppm) and mass spectrum (ion peak with m/e 150 corresponding to splitting out of pyrrolidone [M-85]).

The amidoalkylation of 2-acetamidonaphthalene (XII) gives 2-acetamido-1-pyrrolidonylmethylenenaphthalene (XIII). We were unable to carry out the reaction with p-diacetylphenylenediamine and p-acetamidobenzoic acid with N-methylolpyrrolidone; the starting reagents were recovered in both cases.

EXPERIMENTAL METHOD

The mass spectra of the compounds were recorded with an MKh-1303 spectrometer. The PMR spectra of CD_3OD solutions were recorded with an MChN-100 spectrometer with tetramethylsilane as the standard. The IR spectra were recorded with a UR-10 spectrometer.

N-Methylolpyrrolidone. This compound was obtained by an improved method [6]. A mixture of 25.5 g (0.3 mole) of pyrrolidone and 24 ml of a formalin solution was refluxed for 5-10 min, after which the solution was evaporated to dryness, and the residue was extracted with benzene. When the benzene solution was cooled, 24.4 g of N-methylolpyrrolidone precipitated. The addition of petroleum ether to the filtrate gave another 9.7 g of product for a total yield of 33.7 g (97.5%) of a product with mp 77-78° (in agreement with [6]).

TABLE 1. Physicochemical Properties of Substituted N-Benzylpyrrolidones

Compound	Reaction temp., °C	mp, °C*	R_f†	Empirical formula	N, % found	N, % calc.	Mol. wt. (mass spectrometrically)	Yield, %
II	20	162—163	0,24	$C_{13}H_{16}N_2O_2$	12,4	12,1	232	44,5
II	70				12,3	12,1	232	40,2
III	70	124—125	0,50	$C_{13}H_{16}N_2O_2$	12,3	12,1	232	5,0
VI	20	132—133	0,32	$C_{14}H_{18}N_2O_2$	11,4	11,4	246	37,0
VIII	20	122	0,95	$C_{14}H_{18}N_2O_2$	11,5	11,4	246	38,0
IX	20	158—160	0,65	$C_{14}H_{18}N_2O_2$	11,5	11,4	246	27,0
X	20	175—176	0,14	$C_{13}H_{16}N_2O_3$	11,5	11,3	248	33,0
XI	80	179—181	0,58	$C_{11}H_{13}N_3O_3$	17,9	17,9	235	50,0
XII	20	240—242	0,47	$C_{17}H_{18}N_2O_2$	10,1	9,9	282	22,0

*Crystallization solvents: benzene for II, VI, IX, X and XII, hexane for III, ether for VIII, and water for XI.
†Thin-layer chromatography on silica gel in a chloroform—methanol system (25:1).

Condensation of Acetanilide with N-Methylolpyrrolidone. A 2.7-g (0.02 mole) sample of acetanilide and 2.3 g (0.02 mole) of I were added successively in portions to 10 ml of concentrated H_2SO_4, after which the mixture was stirred at room temperature for 1 h and allowed to stand overnight. It was then poured over ice, and the mixture was extracted with chloroform. The chloroform extract was dried over calcined magnesium sulfate, the chloroform was removed, and the residue was recrystallized from benzene to give 2.0 g (44.5%) of II with mp 162-163°.

Condensation of Acetanilide with N-Methylolpyrrolidone at 70°. The reaction was carried out at 70° for 1 h, after which the mixture was worked up as in the preceding experiment to give 1.9 g (40.2%) of II with mp 162-163°. To isolate III, the benzene solution was evaporated to dryness, and the residue was recrystallized from hexane to give 0.3 g (5%) of III with mp 124-125°.

The condensations of substituted acetanilides with I at a molar ratio of 1:1 were carried out under similar conditions. Some of the physicochemical properties of the compounds obtained are presented in Table 1.

Hydrolysis of o-Acetamidobenzylpyrrolidone (III). A mixture of 0.4 g (0.002 mole) of III and 2.9 ml of concentrated HCl was heated on a water bath for 1 h, after which it was cooled and made alkaline with ammonium hydroxide. The alkaline mixture was extracted with ether, the extract was dried with anhydrous magnesium sulfate, and the ether was removed by distillation. The residue was recrystallized from benzene–petroleum ether to give 0.1 g (32%) of o-aminobenzylpyrrolidone (IIIa) with mp 72-73° (in agreement with [7]).

1,3-Trimethylene-3,4-dihydroquinazoline (IV). A mixture of 0.08 g (0.4 mmole) of o-aminobenzylpyrrolidone and 0.5 ml of phosphorus oxychloride was heated on a water bath for 1 h, after which it was decomposed with water and made alkaline with ammonium hydroxide. It was then extracted with chloroform, and the chloroform extract was dried with anhydrous magnesium sulfate. The chloroform was evaporated, and the residue was recrystallized from petroleum ether to give 25 mg (35%) of IV with mp 86-87° (in agreement with [8]). Molecular weight 172 (by mass spectrometry).

Hydrolysis of 5-Acetamido-2-methylbenzylpyrrolidone (VI). A 2.5-g (0.01 mole) sample of VI was refluxed in 10 ml of concentrated HCl for 1 h, after which it was cooled, made alkaline with 25% ammonium hydroxide, and extracted with ether. The extract was dried with anhydrous sodium sulfate, the ether was removed by distillation, and the residue was recrystallized from benzene to give 1.4 g (68%) of 5-amino-2-methylbenzylpyrrolidone (VII) with mp 110-111°. Found: N 13.6%. M 204 (mass spectrometrically). $C_{12}H_{16}N_2O$. Calculated: N 13.7%. M 204.

Reaction of Benzylpyrrolidone VII with Phosphorus Oxychloride. A 1-ml sample of phosphorus oxychloride was added with stirring to a solution of 0.9 g (0.004 mole) of VII in 10 ml of absolute benzene. The mixture took on a red coloration, and an oil began to

separate. Stirring was continued for 2 h, after which the benzene layer was decanted, and the residue was dissolved in water. The solution was made alkaline with ammonium hydroxide and extracted with chloroform. The extract was dried with magnesium sulfate, the chloroform was removed by distillation, and the residue began to crystallize on standing. Recrystallization from benzene gave 0.64 g of starting 5-amino-2-methylbenzylpyrrolidone VII with mp 111-112° (no melting-point depression was observed for a mixture of this product with a genuine sample). Both samples had R_f 0.79 [chloroform–methanol (25:1)] during chromatography in a thin layer of silica gel.

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