SYNTHESIS OF 7-BENZYL-3-OXO-7H,1,2,3,4,5,6-HEXAHYDROPYRROLO[2,3-c]PYRIDAZINE

L. N. Yakhontov, M. Ya. Uritskaya, and R. G. Glushkov

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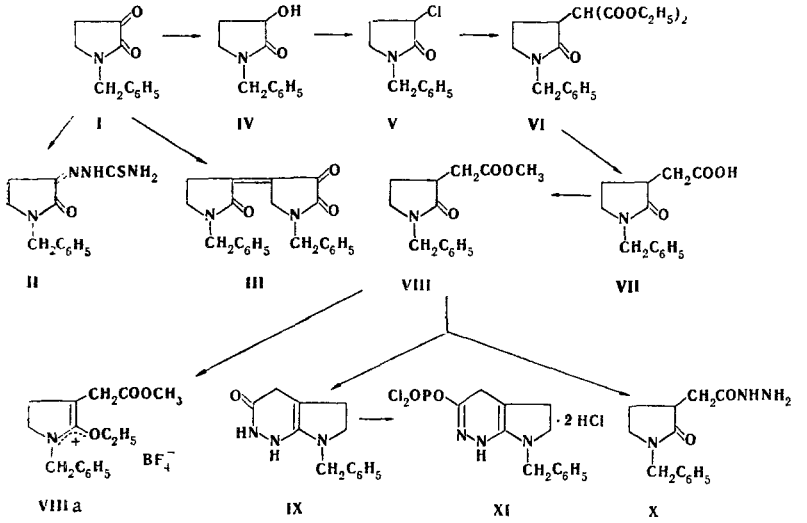
7-Benzyl-3-oxo-7H,1,2,3,4,5,6-hexahydropyrrolo[2,3-c]pyridazine was synthesized from 1-benzyl-2,3-dioxopyrrolidine through the corresponding 3-hydroxy, 3-chloro, 3-(diethoxycarbonyl)methyl, and 3-ethoxycarbonylmethyl derivatives. The Fischer cyclization of cyclohexanone 5-chloro-2-pyridazylhydrazone, which leads to 2-chloro-1,9a-diaza-5,6,7,8-tetrahydrocarbazole, was studied.

In contrast to the isomeric pyrrolopyrazine and pyrrolopyrimidine condensed systems, which have been the subject of rather intensive study in recent years in connection with the discovery and study of the antibiotics tubercidin, toyocamycin, and sangivomycin, pyrrolo[2,3-c]pyridazines and the corresponding hydrogenated compounds and their derivatives have not been described in the literature.

We have developed the synthesis of a partially hydrogenated derivative of the pyrrolo[2,3-c]pyridazine system [1] via the following scheme:



1-Benzyl-2,3-dioxopyrrolidine (I), which is obtained as a result of the reaction of methyl acrylate with benzylamine and subsequent cyclization of the resulting β-benzylaminopropionic acid ester with diethyl oxalate [2], was used as the starting compound in this synthesis. Reaction of dioxo compound I with thiosemicarbazide gave the corresponding thiosemicarbazone (II), which, in contrast to its two-ring analog – isatin thiosemicarbazone (the preparation methisazone) – does not have antivirus activity. When the Reformatskii reaction was carried out with zinc and the bromoacetate of I, it underwent a considerable degree of self-condensation to give 1-benzyl-2,3-dioxo-4-(1'-benzyl-2'-oxo-3'-pyrrolidylidene)pyrrolidine (III) due to the high reactivity of the methylene group in the α position relative to the ketone carbonyl group. In this connection, the malonic ester synthesis was used to obtain the compound with an acetic acid residue in the 3 position of the pyrrolidine ring. The 3-oxo group in dione I underwent selective reduction to a hydroxyl group. In contrast to the method

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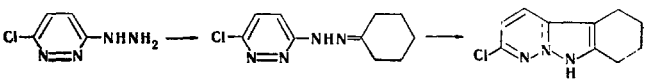
of catalytic hydrogenation in the presence of platinum described in [3], we used the preparatively more convenient reduction with sodium borohydride. The 1-benzyl-2-oxo-3-hydroxypyrrolidine (IV), which was obtained in 77.5% yield, was converted by the action of thionyl chloride at room temperature to the corresponding 3-chloro derivative (V), which reacted with sodium malonic ester to give 1-benzyl-2-oxo-3-(diethoxycarbomylmethyl)pyrrolidine (VI). Saponification and partial decarboxylation of diester VI by refluxing for 4 h with 18% hydrochloric acid did not involve the amide group [the reaction was monitored by thin-layer chromatography (TLC)] and made it possible to obtain acid VII in quantitative yield. It was subsequently found that it was more convenient not to isolate acid VII in pure form but rather to directly esterify it to 1-benzyl-2-oxo-3-methoxycarbonylmethylpyrrolidine (VIII). It was necessary to subject the ring amide group to prior activation in order to close the partially hydrogenated pyridazine ring on the basis of amido ester VIII and hydrazine hydrate. For this, VIII was converted by treatment with triethyloxonium tetrafluoroborate to the corresponding tetrafluoroborate complex (VIIIa), which we were also able to cyclize to 7-benzyl-3-oxo-7H,-1,2,3,4,5,6-hexahydropyrrolo[2,3-c]pyridazine (IX). When it was not converted to the terafluoroborate complex (VIIIa), cyclization of amido ester VIII with hydrazine in benzene, xylene, acetone, and alcohols at room temperature and by heating did not give positive results. The yield of the two-ring product was only 30-40% even when tetrafluoroborate complex VIIIa was heated to 160°; 30% VIII was converted to monocyclic hydrazide X, which was converted to IX by heating to the boiling point with phosphorus oxychloride. Compound IX undergoes destruction during dehydrogenation or under the influence of reducing agents under severe conditions, but, like some cyclic amines [4], it is capable of undergoing conversion to an O-dichlorophosphoryl derivative on treatment with phosphorus oxychloride. Compound XI was obtained in quantitative yield; it is reconverted to IX on treatment with water and alcohol.

It is interesting to note that in the Fischer cyclization of cyclohexanone 5-chloro-2-pyridazylhydrazone (XII), instead of the normal indolization to give a partially hydrogenated condensed diazaindole system, the compound undergoes cyclization at the azine nitrogen atom, and a new heterocyclic system of a partially hydrogenated 2-chloro-1,9a-diazacarbazole (XIII) is formed; this is due to the increased electron density on the nitrogen atom of the pyridazine ring and the reduced density of the electrons on the carbon atoms of the diazine ring, as also occurs in the case of 2-pyridylhydrazones [5].



XII XIII

The reaction in the presence of the most active catalyst of the Fischer reaction in azine systems – zinc chloride [6] – occurs only under very severe conditions – at 250-260°. The less stable cyclohexanone 2-pyridazylhydrazone, which does not have a stabilizing chlorine atom in the 5 position, undergoes complete resinification under these conditions.

EXPERIMENTAL

1-Benzyl-2,3-dioxopyrrolidine Thiosemicarbazone (II). A solution of 1 g (5 mmole) of I in 10 ml of 96% alcohol was added to a solution of 0.48 g (5 mmole) of thiosemicarbazide in 10 ml of 50% ethanol, and the mixture was refluxed for 30 min. The resulting precipitate was removed by filtration to give 1.15 g (83.5%) of white crystals of thiosemicarbazone II with mp 214-215° (from aqueous alcohol). The product was only slightly soluble in alcohol and other ordinary organic solvents but was more soluble in water. Found: C 55.1; H 5.2; N 21.6; S 12.1%. $C_{12}H_{14}N_4SO$. Calculated: C 55.0; H 5.3; N 21.4; S 12.2%.

1-Benzyl-2,3-dioxo-4-(1'-benzyl-2'-oxo-3'-pyrrolidylidene)pyrrolidine (III). A solution of 1 g (5 mmole) of dioxo compound I in 10 ml of anhydrous benzene was added to a mixture of 1.86 g (11 mmole) of bromoacetic ester and 0.72 g (11 mmole) of zinc dust in 50 ml of anhydrous benzene, and the mixture was refluxed for 3 h with monitoring of the disappearance of starting I by thin-layer chromatography (TLC). The resulting precipitate was removed by filtration and recrystallized from benzene to give 0.5 g (28%) of colorless crystals of III with mp 174-175°. The product was soluble in alcohol and chloroform but only slightly soluble in ether, benzene, and water. Found: C 73.6; H 6.0; N 7.5%. $C_{22}H_{20}N_2O_3$. Calculated: C 73.5; H 5.6; N 7.8%.

1-Benzyl-2-oxo-3-hydroxypyrrolidine (IV). A 2.4-g (63 mmole) sample of sodium borohydride was added in portions with constant stirring to a solution of 4.6 g (24 mmole) of dioxo compound I in 15 ml of methanol, and the mixture was then stirred at room temperature for 20 min. Water (50 ml) was added, and IV was extracted with chloroform. The residue remaining after removal of the chloroform by distillation was recrystallized from cyclohexanone to give 3.6 g (77.5%) of colorless crystals of IV with mp 69-70° [3].

1-Benzyl-2-oxo-3-chloropyrrolidine (V). A 1-ml (14 mmole) sample of thionyl chloride was added dropwise to 2.1 g (11 mmole) of hydroxy derivative IV dissolved in 15 ml of anhydrous chloroform, and the mixture was allowed to stand at room temperature overnight. It was then evaporated to dryness, and the thionyl chloride residue was removed by distillation with benzene. The residue was distilled at 156-157° (2 mm) to give 1.9 g (82.6%) of colorless crystals of V with mp 51-52°. The product was soluble in chloroform and alcohols but only slightly soluble in ether and water. Found: C 63.1; H 5.8; Cl 16.9; N 6.8%. $C_{11}H_{12}ClNO$. Calculated: C 63.0; H 5.7; Cl 17.0; N 6.7%.

1-Benzyl-2-oxo-3-(diethoxycarbonylmethyl)pyrrolidine (VI). A 5-g (22 mg-atom) sample of sodium was pulverized in 30 ml of anhydrous xylene, after which 5 ml (31 mmole) of malonic ester was added, and the mixture was allowed to stand at room temperature for 30 min. It was then heated at 100° until the chunks of sodium metal vanished completely. A 2.5-g (12 mmole) sample of chloride V was then added, and the mixture was refluxed for 4 h. It was then treated with 10 ml of water, and the xylene layer was separated. The aqueous layer was extracted with chloroform, the combined extracts were dried with magnesium sulfate, and the solvent was vacuum evaporated. The residue was distilled at 210-212° (2 mm) to give 2.8 g (70%) of diester VI. Found: C 64.6; H 6.9; N 4.2%. $C_{18}H_{23}NO_5$. Calculated: C 64.8; H 6.9; N 4.2%.

1-Benzyl-2-oxo-3-carboxymethylpyrrolidine (VII). A solution of 2.8 g (8 mmole) of diester VI in 10 ml of 18% hydrochloric acid was refluxed for 4 h with monitoring of the end of saponification and partial decarboxylation by TLC. The hydrochloric acid was removed by vacuum evaporation to give 1.96 g (100%) of VII with bp 214-215° (3 mm). The product was only slightly soluble in ether, benzene, and chloroform but more soluble in alcohols, water, and acetone. Found: C 66.8; H 6.5; N 5.9%. $C_{13}H_{15}NO_3$. Calculated: C 67.0; H 6.4; N 6.0%.

1-Benzyl-2-oxo-3-methoxycarbonylmethylpyrrolidine (VIII). A 6.4-g (19 mmole) sample of diester VI was refluxed in 20 ml of 18% hydrochloric acid, after which the solution was vacuum evaporated to dryness, and 5 ml of anhydrous chloroform and 4 ml (56 mmole) of thionyl chloride were added to the residue. The mixture was allowed to stand at room temperature overnight, after which it was vacuum evaporated to dryness. The thionyl chloride residues were removed by distillation with benzene, after which 10 ml of methanol was added, and the mixture was refluxed for 3 h. It was then vacuum evaporated, and the residue was treated with 50% aqueous potassium carbonate solution and extracted with benzene. The benzene extract was dried with magnesium sulfate and vacuum evaporated, and the residue was fractionated to give 3 g (63%) of VIII with bp 176-178° (2 mm). Found: C 68.0; H 7.0; N 5.7%. $C_{14}H_{17}NO_3$. Calculated: C 67.9; H 6.9; N 5.7%.

7-Benzyl-3-oxo-7H,1,2,3,4,5-hexahydropyrrolo[2,3-c]pyridazine (IX). A) A solution of 3.6 g (14 mmole) of amido ester VIII in 5 ml of anhydrous chloroform was added with stirring to a cooled (to 0°) solution of 3.3 g (23 mmole) of triethyloxonium tetrafluoroborate in 10 ml of anhydrous chloroform, and the mixture was stirred at room temperature for 3 h and allowed to stand overnight. It was then vacuum evaporated, and 0.8 g (16 mmole) of hydrazine hydrate was added. The mixture was then stirred as the temperature was gradually raised in the course of 1.5 g to 160°. It was then cooled and treated with 5 ml of 20% sodium hydroxide solution. Compound IX was extracted with benzene. The benzene extract was dried with magnesium sulfate and vacuum evaporated to dryness to give 1 g (31%) of IX with mp 179-181°. Found: C 67.7; H 6.6%. $C_{13}H_{15}N_3O$. Calculated: C 68.1; H 6.6%. The hydrochloride was obtained as colorless crystals; with mp 189-190°, that were quite soluble in alcohols and water but only slightly soluble in acetone, ether, and benzene. Found: C 58.5; H 6.0; Cl 13.3; N 15.7%. $C_{13}H_{15}N_3O$. Calculated: C 58.7; H 6.0; Cl 13.4; N 15.8%.

Additional extraction with chloroform yielded 1.89 g (53%) of X as colorless crystals with mp 104-105° (from ether). Found: C 63.2; H 7.2; N 17.0%. $C_{13}H_{17}N_3O_2$. Calculated: C 63.1; H 6.9; N 17.0%.

B) A 0.4-g (1.6 mmole) sample of hydrazide X was refluxed with 1 ml of phosphorus oxychloride for 30 min, after which the mixture was poured over ice, and the aqueous mixture was made alkaline with 50% aqueous potassium carbonate solution and extracted with benzene. Removal of the benzene by distillation gave 0.25 g (67%) of IX with mp 179-181°. No melting-point depression was observed for a mixture of this product with a sample of IX obtained by method A. The IR spectra of the two samples were identical.

7-Benzyl-3-dichlorophosphoryloxyl-1,4,5,6-tetrahydropyrrolo[2,3-c]-pyridazine Dihydrochloride (XI). A mixture of 0.1 g (0.4 mmole) of IX and 2 ml of freshly distilled phosphorus oxychloride was heated at 80-90° for 2 h, after which it was diluted with 10 ml of anhydrous ether. The precipitated yellow crystals of XI were removed by filtration to give 0.15 g (quantitative yield) of a product with mp 134-135°. The product was only slightly soluble in ether and benzene and was converted to starting IX by the action of water or alcohol. Found: C 37.7; H 4.0; N 10.3%. $C_{13}H_{14}Cl_2N_3O_2P \cdot 2HCl$. Calculated: C 37.3; H 3.6; N 10.1%.

Cyclohexanone 5-Chloro-2-pyridazylhydrazone (XII). A 2-g (14 mmole) sample of 5-chloro-2-hydrazinopyridazine was triturated thoroughly with 3 ml (30 mmole) of cyclohexanone, and the mixture was allowed to stand at room temperature for 30 min. It was then treated with 3 ml of methanol, and the precipitated XII was removed by filtration to give 2.6 g (84%) of colorless crystals with mp 149-150° (from alcohol). The product was only slightly soluble in ether and benzene but was more soluble in chloroform, alcohols, and acetone. Found: C 53.5; H 5.7; N 24.7%. $C_{10}H_{13}ClN_4$. Calculated: C 53.5; H 5.8; N 24.9%.

2-Chloro-5,6,7,8-tetrahydro-1,9a-diazacarbazole (XIII). A 9-g (40 mmole) sample of hydrazone XII was stirred with 18 g (130 mmole) of fused zinc chloride, and the mixture was quickly placed in a Wood's metal bath heated to 250°. After the onset of the exothermic reaction, the flask was quickly removed from the bath and allowed to stand until the markedly exothermic process was complete. The reaction was then brought to completion by heating at 250-260° for 1-2 min in a Wood's metal bath. It was then cooled and dissolved in 50 ml of concentrated hydrochloric acid, and the solution was treated with 50 ml of water. The nonresinified reaction products were extracted with ether, and the ether extract was dried with magnesium sulfate and evaporated to give 1.7 g (25%) of yellow crystals of XIII with mp 133-134° (from ether) and bp 183-184° (1.5 mm). The product was quite soluble in most of the ordinary organic solvents but only slightly soluble in water and ether. Found: C 57.8; H 4.9; Cl 16.8; N 20.4%. $C_{10}H_{10}ClN_3$. Calculated: C 57.8; H 4.8; Cl 17.1; N 20.2%. Additional extraction with chloroform yielded 1.6 g (35.6%) of starting XII.

Nonobservance of the temperature conditions indicated in the above description, an increase in the heating time, and an increase in the amount of zinc chloride led to considerably greater resinification of the reaction products.

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